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# RELATIONSHIP OF TONSILS AND ADENOIDS TO THE TYPE OF POLIOMYELITIS

## AN ANALYSIS OF FOUR HUNDRED AND THIRTY-TWO CASES

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PHILADELPHIA

Since Ayer,[1] in 1928, and Aycock and Luther,[2] in 1929, reported instances of poliomyelitis following recent tonsillectomy, there have been a number of papers on this subject. Many of the observers were able to show that the removal of tonsils and adenoids during a season in which poliomyelitis was prevalent made the patient more susceptible to the disease, and they considered the operative wound as a portal of entry for the virus.

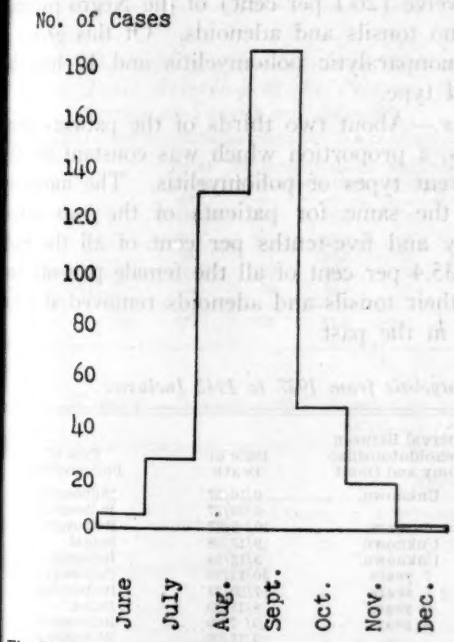


Fig. 1.—Monthly distribution of time of onset of poliomyelitis for 432 cases occurring from 1937 to 1942 inclusive.

Fischer, Stillerman and Marks [3] and Top and Vaughan [4] have since studied the status of tonsils and adenoids relative to the incidence of acute poliomyelitis and have observed that tonsils and adenoids were frequently absent in patients with involvement of the higher centers. The purpose of the present study is to determine the relationship that the presence or absence of tonsils bears to the type of disease acquired and to mortality.

### MATERIAL

The material for this study included 432 patients admitted to the Philadelphia Hospital for Contagious Diseases with acute anterior poliomyelitis from 1937 to 1942 inclusive. The number of patients admitted yearly ranged from 9 to 177, and the monthly distribution was the same each year, that is, admissions during August and September predominated (fig. 1).

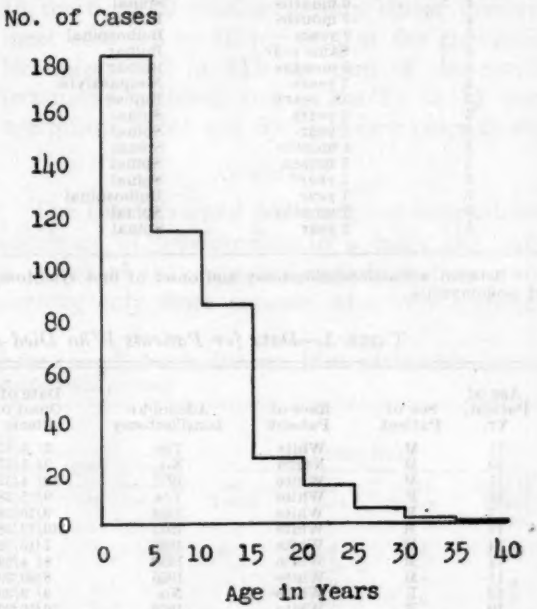


Fig. 2.—Distribution of 432 cases of poliomyelitis according to the ages of the patients.

From the Philadelphia Hospital for Contagious Diseases.

1. Ayer, W. D.: Poliomyelitis, Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America **9**:319, 1928.

2. Aycock, W. L., and Luther, E. H.: The Occurrence of Poliomyelitis Following Tonsillectomy, New England J. Med. **200**:164 (Jan. 24) 1929.

3. Fischer, A. E.; Stillerman, M., and Marks, H. H.: Relation of Tonsillectomy and of Adenoidectomy to the Incidence of Poliomyelitis, with Special Reference to the Bulbar Form, Am. J. Dis. Child. **61**:305 (Feb.) 1941.

4. Top, F. H., and Vaughan, H. F.: Epidemiology of Poliomyelitis in Detroit in 1939, Am. J. Pub. Health **31**:777 (Aug.) 1941.

TABLE 1.—*Seasonal Distribution of the Types of Poliomyelitis Based on the Records of Four Hundred and Twenty-Seven Patients (1937 to 1942 Inclusive)*

| Type of Poliomyelitis | Adenotonsillar Status of Patient | June | July | Aug. | Sept. | Oct | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|
| Spinal | T&A * | 3 | 1 | 36 | 40 | 13 | 5 | .. | 98 |
| | None | 3 | 22 | 62 | 88 | 33 | 9 | 2 | 219 |
| Bulbar | T&A | .. | .. | 8 | 11 | 3 | 1 | .. | 23 |
| | None | .. | .. | 2 | 3 | 2 | .. | .. | 7 |
| Bulbospinal | T&A | .. | 1 | 6 | 13 | 6 | 1 | 1 | 28 |
| | None | .. | 3 | 5 | 7 | 1 | 2 | .. | 18 |
| Nonparalytic | T&A | .. | .. | 6 | 8 | .. | 1 | .. | 15 |
| | None | .. | .. | 5 | 14 | 0 | .. | .. | 19 |

* T&A indicates patients who had had adenoidotonsillectomy. None indicates patients who had not had adenoidotonsillectomy.

TABLE 2.—*Types of Poliomyelitis Occurring in Nineteen Tonsillectomized Patients Under Six Years of Age*

| Age of Patient, Yr. | Interval * | Type of Poliomyelitis |
|---|---|---|
| 2 | 1 year | Bulbar |
| 4 | Unknown | Spinal |
| 4 | 1 year | Spinal |
| 4 | 3 weeks | Bulbospinal |
| 4 | 6 months | Spinal |
| 4 | 3 months | Bulbar |
| 5 | 2 years | Bulbospinal |
| 5 | Same year | Bulbar |
| 5 | 5 months | Bulbar |
| 5 | 2 years | Nonparalytic |
| 5 | 1½ years | Bulbar |
| 5 | 2 years | Spinal |
| 5 | 1 year | Spinal |
| 5 | 4 months | Spinal |
| 5 | 1 month | Spinal |
| 5 | 1 year | Spinal |
| 5 | 1 year | Bulbospinal |
| 5 | 7 months | Spinal |
| 5 | 1 year | Spinal |

* Between adenoidotonsillectomy and onset of first symptom of poliomyelitis.

cord are involved is classified as "bulbospinal poliomyelitis." Poliomyelitis without weakness or paralysis is referred to as "nonparalytic."

*Season.*—The type of poliomyelitis that occurred was related to the season; that is, spinal poliomyelitis, which is the most common type, was the first to appear (July and August) and the last to disappear (November and December), whereas bulbar, bulbospinal and nonparalytic poliomyelitis more frequently appeared in August and September, when the season was at its height.

*Race.*—Of the total number of patients 10.9 per cent were Negroes and 89.1 per cent were white. The percentage of Negroes in the total population under 15 years of age according to the 1940 census for Philadelphia was 15.6. Five of the 48 patients with bulbospinal poliomyelitis and 8 of the 35 with nonparalytic poliomyelitis were Negroes. There were no Negroes with the bulbar type.

Twelve (26.1 per cent) of the Negro patients had no tonsils and adenoids. Of this group 2 had nonparalytic poliomyelitis and 10 had the spinal type.

*Sex.*—About two thirds of the patients were males, a proportion which was constant for the different types of poliomyelitis. The mortality was the same for patients of the two sexes. Forty and five-tenths per cent of all the male and 35.4 per cent of all the female patients had had their tonsils and adenoids removed at some time in the past.

TABLE 3.—*Data for Patients Who Died of Poliomyelitis from 1937 to 1942 Inclusive*

| Age of Patient, Yr. | Sex of Patient | Race of Patient | Adenoidotonsillectomy | Date of Onset of Illness | Interval Between Adenoidotonsillectomy and Onset | Date of Death | Type of Poliomyelitis |
|---|---|---|---|---|---|---|---|
| 11 | M | White | Yes | 9/ 5/37 | Unknown | 9/10/37 | Bulbospinal |
| 10 | M | Negro | No | 9/ 5/37 | — | 9/12/37 | Bulbospinal |
| 11 | M | White | 1931 | 10/ 4/37 | 6 years | 10/ 5/37 | Bulbospinal |
| 21 | F | White | Yes | 9/ 5/38 | Unknown | 9/13/38 | Spinal |
| 7 | F | White | 1938 | 9/10/38 | Unknown | 9/13/38 | Bulbospinal |
| 12 | M | White | 1931 | 10/12/38 | 7 years | 10/13/38 | Bulbospinal |
| 14 | M | White | 1932 | 7/15/32 | 7 years | 7/30/39 | Bulbospinal |
| 14 | M | White | 1930 | 8/ 4/39 | 9 years | 8/12/39 | Bulbar |
| 11 | M | White | 1935 | 8/30/39 | 4 years | 9/ 7/39 | Bulbospinal |
| 16 | F | White | No | 9/ 9/39 | — | 9/13/39 | Blubospinal |
| 10 | F | White | 1936 | 10/16/39 | 3 years | 10/21/39 | Bulbospinal |
| 14 | M | White | No | 10/11/39 | — | 10/16/39 | Spinal |
| 10 | F | White | 1938 | 9/ 7/40 | 2 years | 9/11/40 | Bulbar |
| 2 | M | White | No | 9/ 3/40 | — | 9/ 6/40 | Spinal |
| 12 | M | White | 1936 | 9/25/40 | 4 years | 9/30/40 | Bulbar |
| 11 | M | White | 1931 | 9/24/40 | 9 years | 10/29/40 | Spinal |
| 24 | M | White | 1928 | 9/27/40 | 12 years | 11/30/40 | Spinal |
| 30 | F | White | 1940 | 12/31/40 | Unknown | 1/ 5/41 | Bulbospinal |

## THE TYPES OF POLIOMYELITIS AND THEIR RELATIONS TO VARIOUS FACTORS

The term "spinal poliomyelitis" is used to designate the condition in which only the spinal cord is involved. The term "bulbar poliomyelitis" is used for the condition in which cranial nerves only are involved. The condition in which both the cranial nerves and the spinal

*Age of the Patient.*—Patients under 6 years constituted the largest age group. The incidence of the disease had an inverse relationship to age. The youngest patient was 8 months old, and the oldest was 38 (fig. 2).

*Tonsillectomy and Adenoidectomy.*—Data on tonsillectomies and adenoidectomies were not obtained in 5 of the 432 cases. There were 19

patients under 6 years of age who had had their tonsils and adenoids removed, and 8 of these children (41 per cent) had bulbar involvement. On the other hand, of 161 patients in the nonadenoidotonsillectomized group under 6 years of age, only 13 (8.1 per cent) had bulbar involvement.

*Mortality.*—Eighteen of 432 patients died. Of these 3 had bulbar, 5 had spinal and 10 had bulbospinal poliomeningitis. Fourteen of the patients who died (78 per cent) had had tonsillectomy and adenoidectomy.

TABLE 4.—*Mortality According to the Types of Poliomyelitis*

| Type | Number of Cases | Number of Deaths | Number of Deaths per Hundred Cases |
|---|---|---|---|
| Spinal | 319 | 5 | 1.6 |
| Bulbar | 30 | 3 | 10.0 |
| Bulbospinal | 48 | 10 | 20.8 |
| Nonparalytic | 35 | 0 | 0.0 |
| Total | 432 | 18 | 4.2 |

TABLE 5.—*Incidence of Poliomyelitis of Each of the Four Types According to the Presence or Absence of Tonsils and Adenoids*

| Type | Total Number of Patients | Patients Without Tonsillectomy | | Patients With Tonsillectomy | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Spinal | 317 | 219 | 69.1 | 98 | 30.9 |
| Bulbar | 30 | 7 | 23.3 | 23 | 76.7 |
| Bulbospinal | 46 | 18 | 39.1 | 28 | 60.9 |
| Nonparalytic | 34 | 19 | 55.9 | 15 | 44.1 |
| Total | 427 | 263 | 61.6 | 164 | 38.4 |

Over 76 per cent of the patients with bulbar poliomyelitis and 61 per cent of those with bulbospinal poliomyelitis had had an adenoidotonsillectomy, while only 30.9 of the patients with only spinal involvement had had their tonsils and adenoids removed. Nonparalytic poliomyelitis occurred in about equal proportions of the adenoidotonsillectomized and the nonadenoidotonsillectomized patients.

There is a greater tendency toward involvement of the higher centers in poliomyelitis in patients without tonsils and adenoids. Table 6 shows that the higher incidence of bulbar and bulbospinal poliomyelitis in patients without tonsils and adenoids occurs in all age groups but is least pronounced in the group over 15 years of age.

In the 0 to 5 years age group only 8.1 per cent of the nontonsillectomized patients had bulbar or bulbospinal poliomyelitis, as against 42 per cent of the tonsillectomized patients; this age group presents the greatest contrast in the incidence of involvement of the higher centers. In the 6 to 10 year age group bulbar involvement occurred in 16 per cent of the nontonsillectomized and in 33.9 per cent of the tonsillectomized patients, and in the 11 to 15 year age group, in 9.7 and 33.2 per cent respectively.

## COMMENT

The data reviewed represent the nonepidemic incidence of poliomyelitis in a large city over a period of six years and include material concerning only those patients who were admitted to the Philadelphia Hospital for Contagious Diseases. In the same period 544 cases and 38 deaths were reported to the city health department. Admittedly the number of cases studied is small, but the consistency of the data adds weight to the belief that a positive correlation exists between absence of pharyngeal lymphoid

TABLE 6.—*Incidence of Poliomyelitis of Each of the Four Types in Patients With (165) and Without (262) Adenoidotonsillectomy*

| | Number of Cases | | | | | | | | Percentage | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0-5 Years | | 6-10 Years | | 11-15 Years | | Over 15 Years | | | | | |
| | M | F | M | F | M | F | M | F | 0-5 Years | 6-10 Years | 11-15 Years | Over 15 Years |
| **Patients without adenotonsillectomy** | | | | | | | | | | | | |
| Spinal | 91 | 46 | 16 | 21 | 16 | 10 | 9 | 9 | 85.1 | 74.0 | 83.8 | 90.0 |
| Bulbar | 2 | 2 | 3 | .. | .. | .. | .. | .. | 2.5 | 6.0 | .... | .... |
| Bulbospinal | 6 | 3 | 3 | 2 | 2 | 1 | .. | 1 | 5.6 | 10.0 | 9.7 | 5.0 |
| Nonparalytic | 7 | 4 | 3 | 2 | 1 | 1 | .. | 1 | 6.8 | 10.0 | 6.5 | 5.0 |
| Total | 106 | 55 | 25 | 25 | 19 | 12 | 9 | 11 | 100 | 100 | 100 | 100 |
| **Patients with adenotonsillectomy** | | | | | | | | | | | | |
| Spinal | 4 | 6 | 20 | 14 | 23 | 8 | 12 | 12 | 52.6 | 54.8 | 57.4 | 80.0 |
| Bulbar | 4 | 1 | 7 | 2 | 7 | .. | 1 | 1 | 26.3 | 14.5 | 13.0 | 6.7 |
| Bulbospinal | 2 | 1 | 9 | 3 | 8 | 3 | .. | 2 | 15.8 | 19.4 | 20.4 | 6.7 |
| Nonparalytic | 1 | .. | 4 | 3 | 5 | .. | 2 | .. | 5.3 | 11.3 | 9.3 | 6.7 |
| Total | 11 | 8 | 40 | 22 | 43 | 11 | 15 | 15 | 100 | 100 | 100 | 100 |

The mortality was lowest for patients with spinal and highest for those with bulbospinal poliomyelitis.

Table 5 shows the incidence of poliomyelitis of each of the four types defined in 164 adenoidotonsillectomized patients and in 263 patients with intact tonsils and adenoids.

tissue and involvement of the higher centers in poliomyelitis.

There has been much criticism of data on this subject by persons who believe that an adenoidotonsillectomy must occur within the incubation period of the disease in order to have any effect on the course of the illness. It is interesting to note that the disease developed within one month after the removal of tonsils and adenoids in only 3 of our patients and that of these 2 had bulbar symptoms.

This review reveals that tonsils and adenoids are absent in a significantly high percentage of patients who have bulbar or bulbospinal poliomyelitis. The absence of adenoidotonsillar tissue apparently increases the likelihood that the bulbar centers will be involved when a susceptible person becomes infected with the virus of poliomyelitis. Hence it may be assumed that Waldeyer's ring inhibits the passage of the virus through the pharyngeal structures. It may be possible that by leaving the tonsils and adenoids in situ the incidence of poliomyelitic infection of the higher centers, which causes the highest mortality, can be reduced. In support of this assumption it will be noted that 78 per cent of the 9 patients in the 11 to 15 year age group who died had bulbar symptoms and had no tonsils or adenoids.

It may be inferred from the evidence in this study that the absence of tonsils and adenoids increases the risk of bulbar and bulbospinal involvement in persons with poliomyelitis. Consequently the indiscriminate removal of tonsils and adenoids should not be condoned. It would be wise to postpone the removal of tonsils and adenoids during the season and in areas in which the incidence of poliomyelitis is abnormally high, if for no other reason than to have these structures act as a protective barrier.

We realize that the relationship between the absence of tonsils and adenoids and the incidence of involvement of the higher centers may be coincidental, that a cause and effect relationship has not been established and that an unknown factor may be the cause.

## SUMMARY AND CONCLUSIONS

Four hundred and thirty-two cases of acute anterior poliomyelitis were reviewed to determine the relationship of the presence or absence of tonsils and adenoids to the type and to the mortality of the disease. The incidence of bulbar and bulbospinal poliomyelitis was significantly higher in patients without than in patients with tonsils and adenoids.

The mortality was 10.9 times greater in the patients with bulbar symptoms than in those with nonbulbar poliomyelitis.

It is recommended that tonsils and adenoids be not removed unless the removal is specifically indicated.

*Addendum:* At the Philadelphia Hospital for Contagious Diseases in 1943 there were 17 cases of poliomyelitis, 1 nonparalytic, 1 bulbar, 3 bulbospinal and 12 spinal. All the patients with bulbar involvement were without tonsils.

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# SULFADIAZINE IN THE TREATMENT OF DIARRHEA IN CHILDREN

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Sulfonamide compounds are more widely used every day for the treatment of diarrhea in children, especially in countries in which infection is the most important cause of diarrhea.

The optimal use of the various sulfonamide compounds in treating the different forms of diarrhea has not yet been determined. New therapeutic agents are being produced rapidly, and the pharmacologists continue to search for new compounds of greater efficiency. It devolves on pediatricians to present clinical observations on the use of these compounds as guides to the value of each preparation.[1] It is for this reason that I wish to record my results with sulfadiazine, following earlier reports on sulfathiazole,[2] sulfaguanidine,[3] and succinylsulfathiazole.[4]

Up to the present time there have been few reports on the use of sulfadiazine in the treatment of diarrhea in children. Abente Haedo and Rodríguez Devincenzi[5] were successful in the treatment of 3 children with bacillary dysentery and 2 with diarrhea due to Salmonella. In June 1943 Richard Tudor[6] published observations on the use of sulfadiazine and sulfapyrazine for infantile diarrhea in which the stools in some cases showed bacillary dysentery. Of the children treated with sulfadiazine, 3 had serious, 4 had moderate and 3 had mild dehydration. The results were satisfactory; the mortality was reduced to zero and the average number of days required for cure was three and nine-tenths.

There are some experimental reports on the action of sulfadiazine against intestinal microorganisms. Strauss and Finland[7] found that sulfathiazole and sulfadiazine were bactericidal against Escherichia coli, Shigella paradysenteriae (Flexner), Salmonella cholerae suis, Salmonella enteritidis, Salmonella Schottmuelleri and Salmonella typhi murium. At a higher concentration they showed bacteriostatic action against Salmonella paratyphi. The same authors, in other experiments on the action of the sulfonamide compounds on E. coli in a synthetic medium, found that sulfadiazine and sulfathiazole were the most active, while sulfapyridine, sulfaguanidine and sulfanilamide were less effective, in the order named.

Neter[8] has produced evidence that sulfadiazine, as well as sulfanilamide, sulfapyridine and sulfaguanidine, is capable of delaying the secondary development of Shigella dysenteriae and E. coli in broth containing bacteriophages.

White[9] tested the activity of various sulfonamide drugs against the intestinal coliform flora. He listed them in the following descending order of activity: sulfapyrazine, sulfadiazine, sulfathiazole, $N^1$-acetylsulfanilamide, sulfaguanidine, sulfanilylarsanilic acid, succinylsulfathiazole and sulfanilamide.

Klinefelter[10] inoculated rats intraperitoneally with a culture of E. coli. They were given 1 per cent of sulfathiazole or 0.7 per cent of sulfadiazine in their food. The latter drug proved more efficacious than the former.

1. Menchaca, F. J.: Los derivados sulfonamídicos en el tratamiento de las diarreas infantiles, Buenos Aires, El Ateneo, 1943, p. 17.

2. Menchaca, F. J.; Moyano Centeno, L., and Albarracín, N.: El sulfatiazol en el tratamiento de las enterocolitis disenteriformes, Arch. argent. de pediat. **15**: 432, 1941.

3. Menchaca, F. J.: La sulfaguanidina en diarreas infantiles de la ciudad de Santa Fe, Arch. argent. de pediat. **16**:473, 1941.

4. Menchaca, F. J.: La nueva sulfonamida: el succinilsulfatiazol en la disentería bacilar y enterocolitis disenteriforme del niño, An. Soc. puericult. Buenos Aires **8**:399, 1942.

5. Abente Haedo, F., and Rodríguez Devincenzi, A.: La sulfadiazina en la shigelosis y en la salmonelosis, An. Fac. de med. de Montevideo **27**:449, 1942.

6. Tudor, R. B.: Chemotherapy of Infantile Diarrhea: Comparison of Sulfadiazine and Sulfapyrazine, J. Pediat. **22**:652, 1943.

7. Strauss, E., and Finland, M.: Bacteriostatic and Bactericidal Action of Sulfadiazine in Vitro on Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **47**: 432, 1941.

8. Neter, E.: Inhibitory Effect of Sulfonamide Compounds upon Development and Growth of Phage-resistant Bacteria, Proc. Soc. Exper. Biol. & Med. **47**:20, 1941.

9. White, H. J.: Comparative Activity of Sulfonamides Against Coliform Bacteria in the Intestine of Mice, Bull. Johns Hopkins Hosp. **71**:213, 1942.

10. Klinefelter, H. F.: Sulfadiazine: Effect on E. Coli Infections in Mice, Proc. Soc. Exper. Biol. & Med. **46**:591, 1941.

In a paper on the activity of sulfathiazole, sulfadiazine, sulfapyrazine and sulfanilamide against E. coli, White, Litchfield and Marshall [11] reported that sulfapyridine was sixteen times and sulfathiazole and sulfadiazine were sixty-four times more active than sulfanilamide.

## PROCEDURE

I decided to employ sulfadiazine [12] for patients with infantile diarrhea entering the children's service under my charge. Most of them had severe or moderate diarrhea that had not improved under treatment in outpatient clinics.

I tried as far as possible to systematize the therapy. Injections of isotonic solution of sodium chloride with dextrose were given, and isotonic solution of three chlorides with 3 per cent dextrimaltose was administered by mouth. The diet consisted of either buttermilk with dextrimaltose or human milk. Only 2 patients received plasma, and the use of antidiarrheics was avoided.

A total of 0.1 to 0.15 Gm. of sulfadiazine per kilogram of body weight was given daily in four doses, six hours apart. I could not begin the treatment with sodium sulfadiazine by intravenous injection, as is recommended for the initial treatment of severe attacks, because the sodium salt was not available.

As is seen in the table of clinical data, there were no deaths. The average time required for recovery was five and nine-tenths days. It is self evident that the determination of the time of recovery was somewhat subjective; however the observations were all made by one person. Dysentery bacilli and salmonellas were absent from the stools (examined by Dr. J. Belloc). There was no sign of intolerance to the drug. In some instances the stools became gray.

## RESULTS

*Table of Clinical Data*

| Patient | Age, Mo. | Weight, Gm | Stools in Last 24 Hr. | Dehydration | Time Required to Improve Stools, Days | Outcome |
|---|---|---|---|---|---|---|
| 1 | 3 | 4,320 | 6 or 7 | Notable | 7 | Recovery |
| 2 | 5 | 7,300 | 6 | Mild | 3 | Recovery |
| 3 | 2 | 3,830 | 7 | Notable | 4 | Recovery |
| 4 | 2 | 3,100 | 7 | Notable | 5 | Recovery |
| 5 | 4 | 5,400 | 6 or 7 | Notable | 15 | Recovery |
| 6 | 3 | 4,520 | 6 | Mild | 12 | Recovery |
| 7 | 17 | 8,000 | 4 | None | 4 | Recovery |
| 8 | 8 | 4,860 | 10 | Notable | 14 | Recovery |
| 9 | 6 | 6,330 | 7 | None | 1 | Recovery |
| 10 | 4 | 3,900 | 7 | Notable | 4 | Recovery |
| 11 | 2 | 3,470 | 7 | Notable | 6 | Recovery |
| 12 | 10 | 6,880 | 17 | Notable | 4 | Recovery |
| 13 | 8 | 7,080 | 3 | Mild | 4 | Recovery |
| 14 | 30 | 13,600 | 6 | Mild | 5 | Recovery |
| 15 | 3 | 4,100 | 5 | Notable | 8 | Recovery |
| 16 | 12 | 6,980 | 7 | Notable | 2 | Recovery |
| 17 | 5 | 3,280 | 3 | Notable | 6 | Recovery |
| 18 | 9 | 5,650 | 8 | None | 3 | Recovery |
| 19 | 5 | 5,930 | 5 | Mild | 3 | Recovery |
| 20 | 5 | 4,610 | 7 or 8 | Notable | 9 | Recovery |

## CONCLUSIONS

From the observation of 20 children with diarrhea treated with sulfadiazine I think that it can be inferred that this drug is an efficacious aid. Further experience will determine the place that it should occupy in the treatment of infantile diarrhea with sulfonamide compounds.

Veinticinco de Mayo 2811.

11. White, H. J.; Litchfield, J. T., Jr., and Marshall, E. K., Jr.: Quantitative Comparisons of Activity of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfadiazine Against Escherichia Coli in Vivo and in Vitro, J. Pharmacol. & Exper. Therap. **73**:104, 1941.

12. The sulfadiazine used was furnished by Lederle Laboratories.

# THUMB AND FINGER SUCKING IN RELATION TO FEEDING IN EARLY INFANCY

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Dr. David M. Levy, a child psychiatrist of New York City, concluded, after a series of clinical studies of children [1] and experiments with animals,[2] that babies suck their thumbs primarily because they do not get enough sucking from breast or bottle.

As a nurse in a Child Health Station of the Department of Health of the City of New York, I had a ready opportunity to test this conclusion. Furthermore, I was sufficiently well acquainted with the mothers who attended the station to be able to select those whose information was reliable. Even so it was necessary, after a preliminary study, to dismiss a number of informants because they were vague about changes in feeding schedules.

Only infants 7 to 8 months of age were selected, and data were collected concerning the feeding schedules followed during the first seven months. Fifteen known thumb suckers and fifteen known non thumb suckers constituted the two groups finally investigated.

Information was obtained as to (1) the type of feeding, breast or formula, (2) the number of feedings per twenty-four hours, (3) the changes in the feeding schedule, (4) the time per feeding and (5) the age of onset of thumb sucking. Questions concerning sucking of bottles containing fluids other than the regular feedings, such as water or orange juice, were not included. No infant in the group used a pacifier. Questions concerning sucking of toys or other objects that may have served the function of pacifiers were also not included. The data are therefore limited to the sucking time in relation to feeding only.

It was found that in general non thumb suckers took a longer time for feeding than was taken by thumb suckers. There were, for example, no infants with a feeding time per day as short as thirty, forty or even sixty minutes at any time in the seven months in the former group, though there were periods of that length in the schedules of 9 infants who sucked their thumbs or fingers. On the other hand, instances of feeding time per day as long as ninety minutes occurred at some time during the seven months in the schedules of all infants who did not suck their thumb or fingers and in the schedules of only 8 of the 15 thumb suckers. If the incidence of long feeding time (ninety minutes or more) in the two groups is compared by units of one month it is seen that in the non-thumb-sucking group average feeding times of this length occurred throughout the seven months in 12 cases, whereas in the thumb-sucking group it occurred throughout the seven months in only 2 cases.

The distribution according to the average feeding time per day during the first seven months for the entire group of 30 infants and for the two subgroups was as follows:

| Average Feeding Time, Min./24 Hr. | Number of Finger Suckers | Number of Non Finger Suckers | Percentage of Finger Suckers |
|---|---|---|---|
| Less than 40..... | 3 | 0 | 100 |
| 40 to 69..... | 5 | 0 | 100 |
| 70 to 99..... | 5 | 5 | 50 |
| 100 to 129..... | 2 | 7 | 22 |
| 130 and over..... | 0 | 3 | 0 |

The relationship between the time spent in feeding and during each day thumb or finger sucking is clearly indicated. In the groups studied the percentage of thumb and finger suckers rose as the feeding time decreased and fell as the sucking time increased.

There is an important condition that is not revealed in the table, namely the onset of thumb and finger sucking after a sudden decrease in the feeding time. In 6 cases thumb and finger sucking began after a diminution of the feeding time occurred; in all but 1 of these, the onset occurred within a day to two weeks after the

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Through the courtesy of the New York City Department of Health, this article was submitted to Dr. David M. Levy as an interesting confirmation of his work on the same subject.

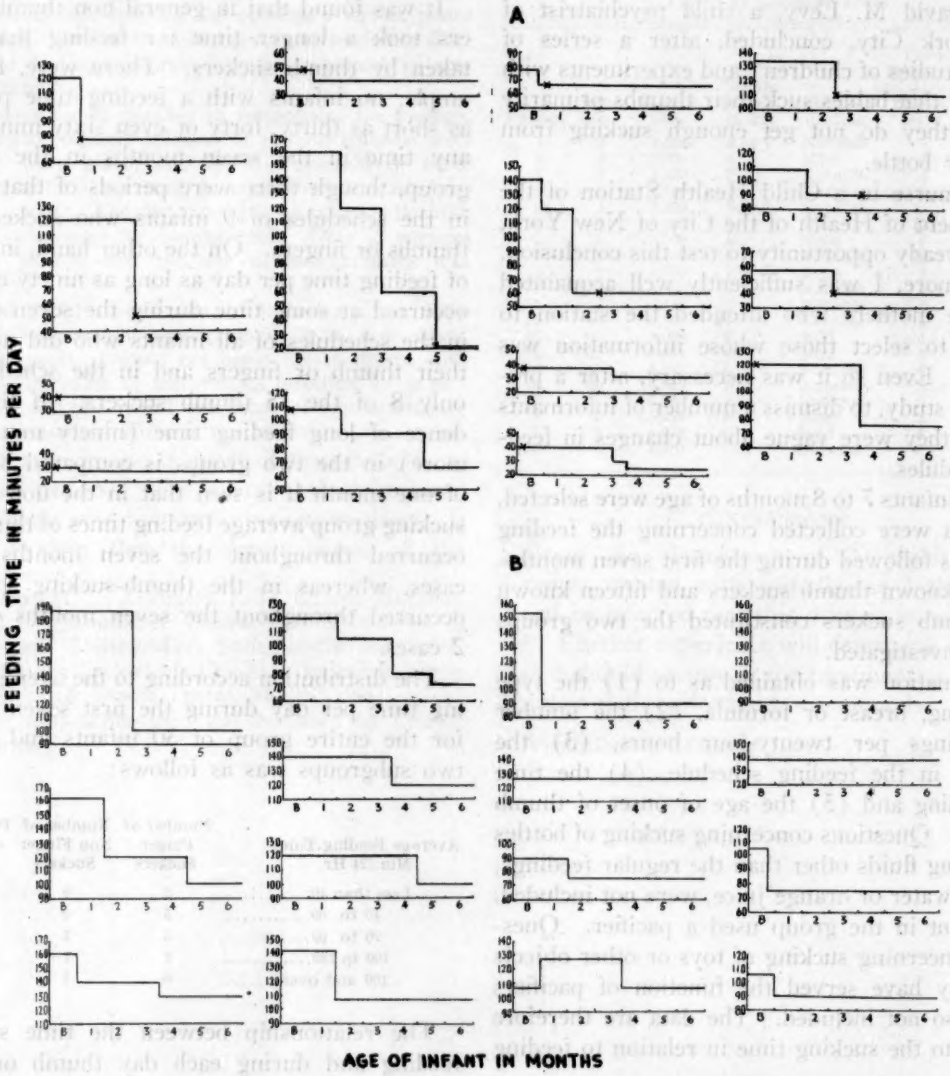
1. Levy, D. M.: Finger-Sucking and Accessory Movements in Early Infancy (An Etiologic Study), Am. J. Psychiat. **7**:811-918, 1928.

2. Levy, D. M.: Experiments on the Sucking Reflex and Social Behavior in Dogs, Am. J. Orthopsychiat. **4**:203-224, 1934; On Instinct-Satiation: An Experiment on the Pecking Behavior of Chickens, J. Gen. Psychol. **18**:327-348, 1938.

change. This relationship may help to explain some instances of thumb and finger sucking in spite of long feeding time if the onset of the habit was preceded by much longer periods of feeding. In 3 cases of thumb sucking in which the feeding time averaged seventy-six, ninety and one hundred and ten minutes the period for feeding had previously averaged one hundred and twenty, one hundred and eight and one hundred and thirty- two minutes respectively. If the criterion of short feeding time in any period within the first seven months is combined with that of decrease in feeding time, only 2 cases of finger sucking are unaccounted for. It will be noted that in the non-finger-sucking group the decrease in the feeding time was gradual and that in only 3 instances was the time reduced to less than eighty minutes per day.

Of 15 thumb and finger suckers, the onset of the habit occurred within the first month of life in 7, in the second month in 2, in the third month in 4, in the fourth month in 1 and in the fifth month in 1. In most of the infants the habit was established in the first two months. One case is interesting in that a gradual reduction in the feeding time occurred without thumb or finger sucking until the total time for feeding was reduced to twenty minutes per twenty-four hours.

This study clearly confirms Dr. Levy's observation that the amount of time spent in sucking is the primary determinant of the habit of sucking the thumb or fingers.




Individual graphs for 30 infants showing the average feeding time per day for each of the first seven months. *A*, charts for infants in whom the habit of thumb sucking developed. The time of onset of thumb sucking is indicated by an X. *B*, charts for infants who did not suck their thumbs or fingers.

# POISONING DUE TO LYE

## VALUE OF BOKAY PROPHYLACTIC DILATION IN PREVENTION OF EARLY STRICTURES OF THE ESOPHAGUS

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Corrosive burns of the esophagus constitute one of the most difficult problems in pediatric practice.[1] Lye is used by poor people as a detergent and in the home manufacture of soap. These people do not realize until it is too late that a solution of lye which will "eat the stains from the boiling kettle" will have a much more dire effect on the oral or esophageal mucosa. As shown by the following series, in 86 per cent of the instances of the accidental use of lye the blame could be directly placed on an adult who carelessly left powdered lye or a solution of lye in a familiar container within the reach of a hungry, thirsty or curious child. In 5 per cent of the instances a child was given a drink from a glass not known to have contained lye, and in 9 per cent the patient took lye with suicidal intent.

At Duke Hospital from 1938 to 1943, 57 patients were treated for poisoning or for burns of the mouth, pharynx, trachea or esophagus due to lye. Fifty others had been reported on for the period from 1930 to 1937,[2] making a total of 107. In the present series 55 patients were poisoned with caustics (potassium hydroxide, sodium hydroxide or ammonium hydroxide), 1 with soap containing lye and 1 with household ammonia. The distribution of the patients according to age is shown in table 1. The 5 oldest patients drank the corrosive with unsuccessful suicidal intent.

From the Departments of Pediatrics and Otolaryngology, Duke University School of Medicine, and Duke Hospital.

1. Brown, H. W., and Kiser, G.: Epidemiology of Lye Poisoning in the United States, Am. J. Pub. Health **32**:822-830 (Aug.) 1942. Tucker, G.: Strictures of the Esophagus: Diagnosis and Treatment, Laryngoscope **41**:426-438 (June) 1931; Cicatricial Stenosis of the Esophagus, with Particular Reference to Treatment by Continuous String, Retrograde Bouginage with the Author's Bougie, Ann. Otol., Rhin. & Laryng. **33**:1180-1214 (Dec.) 1924. Taylor, H. M.: A Preliminary Survey of the Effect Which Lye Legislation Has Had on the Incidence of Esophageal Stricture, ibid. **44**:1157-1158 (Dec.) 1935. Jackson, C.: Cicatricial Stenosis Following the Swallowing of Caustic Alkalis, J. A. M. A. **77**:22-23 (July 2) 1921.

2. Martin, J. M., and Arena, J. M.: Lye Poisoning and Stricture of the Esophagus: A Report of Fifty Cases, South. M. J. **32**:286-290 (March) 1939.

### TREATMENT

*First Aid.*—First aid for persons poisoned with lye should consist in slow oral administration of large amounts (500 cc., 1 pint) of vinegar (diluted with equal parts of water), orange, grapefruit or lemon juice or 2 per cent acetic acid as soon as possible. In this way alkali in the mouth, pharynx and esophagus will be neutralized without sufficient acid entering the stomach rapidly enough to cause vomiting. Then, 1 teaspoon of olive oil should be given every thirty minutes for six hours and every hour for the succeeding twenty-four hours. Removal of the caustic from the stomach by lavage is probably needless, because of the neutralization by gastric hydrochloric acid, and the resulting trauma may be dangerous. For two days after the first aid is given, if liquid can be tolerated, the diet should consist of strained food and liquids every three hours, with ½ teaspoon (about 2.5 cc.) of olive oil between feedings. During the next three days soft, semiliquid foods which are easily swallowed should be given. At the end of this period, after the edema and inflammation have subsided, the esophagus should be carefully and gently visualized by fluoroscopy while the patient is ingesting a small amount of a suspension of barium sulfate or, preferably, with a pharyngoscope (not an esophagoscope, which is dangerous to an esophagus damaged by lye) by a qualified esophagoscopist. In instances in which there is doubt, oral burns from caustic should be considered as presumptive evidence of esophageal burns and as indication enough for Bokay therapy, even though roentgenographic or pharyngoscopic evidence is lacking. If no lesions

TABLE 1.—*Ages at Which the Patients Swallowed the Corrosive Substance*

| Age, Yr. | Patients | |
|---|---|---|
| | Number | Percentage |
| 1 to 2 | 36 | 63 |
| 2 to 5 | 15 | 26 |
| 5 to 10 | 1 | 2 |
| 10 to 20 | 3 | 5 |
| Above 20 | 2 | 4 |

are found or suspected, additional therapy is unnecessary, and the patient may be dismissed, with a warning to report to the hospital if dysphagia occurs. He also should be examined fluoroscopically while swallowing a small amount of a solution of barium sulfate every month for six months in order to detect secondary changes.

The early therapy received by 10 of 57 patients is not known. Thirty-two patients had received vinegar (amounts unknown), 9 had received lard, olive oil or liquid petrolatum and 2 had been given drugs (sulfathiazole or a sedative). The caustic had been removed from the stomachs of 4 patients by lavage.

Four of the patients had had esophageal dilation before admission to Duke Hospital but required gastrostomy and additional dilation. One of the patients had had the esophagus dilated for five days and was admitted with esophageal stenosis one hundred and thirty-five days later; 1 had had dilation every six months for three years but stenosis occurred thirteen years later; 1 had the esophagus dilated for two weeks and was admitted with a stricture ten weeks later, and the fourth had the tube dilated for four weeks, beginning four weeks after the lye had been swallowed, and was admitted later with esophageal stenosis.

Six children in this series were seen at Duke Hospital thirty to one hundred and twenty minutes after the accident and were treated in the dispensary with acid and oil only. Four of them are known to have had no subsequent symptoms of stricture, and 2 did not return for further diagnosis or treatment.

*Bokay Prophylactic Therapy.*—If the presence of oral burns or the conditions revealed by fluoroscopy or pharyngoscopy indicate that the esophagus has been damaged, even slightly, an eyeless (Bokay) catheter,[3] size 10 to 30 (French), which has been filled with lead shot or mercury, tied off at the open end and wet with water or with K-Y lubricating jelly (to avoid the possibility of lipid pneumonia from the use of greasy lubricants) should be gently passed down the child's esophagus (not more than 2 cm. [1 inch] entering the stomach) and left in place for five minutes, once daily,[4] starting on the third day after the child swallows the lye, or as near that time as possible. The catheter should not be forced but allowed to pass merely by weight of the shot or mercury contained in it. This will give adequate force to pass the usual developing stricture without rupturing the esophagus if it should fall into a sacculation. During the first few days the size of the catheter used should be increased until difficulty is encountered in passing it. From the third to the tenth week the largest possible catheter should be passed once daily and kept in place for ten to thirty minutes. The catheter should be introduced twice a week for the next month and then once a week for at least three months; then the interval can be lengthened to suit the patient's condition. I do not mean that the treatment should not be individualized, but the procedure outlined is the safest. The patient should always be warned that the success of the treatment depends on early and continued prophylactic dilation, tedious and uncomfortable though it is.

Unfortunately, only 13 of the patients (23 per cent) were seen in a sufficiently early stage of esophageal damage so that Bokay prophylactic therapy could be used. In the 9 patients for whom Bokay therapy was adequate no strictures of the esophagus occurred (table 3). For 4 children, however, owing to failure of the families to cooperate, the treatment at home was not sufficiently prolonged, and strictures developed, necessitating a second admission to the hospital for gastrostomy and bougienage. It is important to be sure the dilator is completely into the stomach (but not more than 2 cm.), even if it is necessary to use fluoroscopy. In 1 of the patients whose esophagus was not thoroughly dilated a stricture developed at the cardiac orifice while the patient was under treatment. After checking back it was found that the catheter was not long enough to get into the stomach and thus to dilate this low stricture, though two higher strictures were dilated adequately. The average time spent in the hospital by the 9 patients for whom Bokay therapy was successful was twenty-five days, costing $160 per patient at $6.40 per day.

*Bougienage.*—Forty-four of the patients (77 per cent) had esophageal strictures sufficiently severe at the time of admission to the hospital to require bougienage. They did not arrive at the hospital early enough to be given Bokay therapy (not until an average of fifty-six days [5] after the accident). Four others had inadequate Bokay treatment (table 2) and required more radical procedures. If a partial stricture has formed and Bokay dilation cannot be used, a lead-weighted silk thread, to which bougies can subsequently be attached, should be given to the

3. Bokay catheters can be obtained from Murray-Baumgartner Surgical Instrument Co., 5 and 7 West Chase Street, Baltimore, or the eye of an ordinary catheter can be closed at any tire-vulcanizing shop.

4. Bokay, J.: Salzer's Treatment of Lye Poisoning, Wien. klin. Wchnschr. **37**:282-285 (March 30) 1942. Zimanyi, V.: Prophylaxis of Lye Accidents, München. med. Wchnschr. **70**:772 (June 15) 1923.

5. Omitting 5 patients for whom the intervals between the swallowing of lye and the development of the esophageal stricture were three, four, eleven and one-half, twenty and twenty-four years.

patient on repeated occasions until the shot passes into the stomach. This simple but difficult procedure, if done as soon as Bokay therapy is found impossible, will save time and occasionally a life.

TABLE 2.—*Records of Thirteen Patients for Whom Prophylactic Bokay Therapy Was Used*

| Patient No. | Interval Between Swallowing of Lye and Admission to Hospital, Days | Total Days in Hospital | Stricture | Bokay Therapy Continued at Home | Condition (When Last Seen, Either in the Outpatient Clinic or at Discharge From the Hospital) |
|---|---|---|---|---|---|
| 2 | 1 | 35 | No | Yes | Good |
| 3 | 1 (second admission) | 26 (76)† | No Yes | No | Physician could not dilate esophagus because he "had no equipment for it"; gastrostomy and retrograde dilation done |
| 22 | 5 (second admission) | 85 (63)† | No Yes | No | Gastrostomy one and a half months after first discharge, due to stenosis |
| 26 | 1 | 15 | No | No | Condition good at discharge |
| 32 | 6 | 24 | No | No | Condition good twenty-four months after discharge |
| 37 | 1 | 20 | No | No | Good at discharge |
| 40 | 1 (second admission) | 0 (87)† | No Yes | Irregularly | Gastrostomy because patient was not brought to outpatient clinic for regular dilations |
| 42 | 7 (second admission) | 0 (101)† | No Yes | Irregularly | Gastrostomy because patient not treated regularly |
| 46 | 46 | 12 | Yes | Yes | Good |
| 49 | 28 | 9 | No | Yes | Good |
| 51 | 4 | 48 | No | Yes | Good |
| 53 | 2 | 22 | No | Yes | Good |
| 54 | 1 | 40 | No | Yes | Good |

The average stay in the hospital was twenty-five days for patients receiving Bokay therapy without gastrostomy and fifty-one days for patients having secondary gastrostomy.

* All 13 patients on admission had fluoroscopic or esophagoscopic evidence of having swallowed caustic, and 1 had a slight stricture. All except 1 child (no. 32) had had vinegar as the first treatment; no. 32 had water only.

† Second figure indicates duration of the second admission, for secondary gastrostomy.

In half of the patients the strictures were just below the cricopharyngeus muscle, in the upper third of the esophagus, possibly because of spasm of the esophagus when the corrosive irritated it (table 3). All of the patients with strictures required one of the following types of treatment: (1) peroral esophagoscopic bougienage, (2) retrograde bougienage through an artificial gastric fistula or (3) peroral bougienage with a silk thread used as a guide, procedures which involve long hospitalization, inconvenience, expense and the possibility of death from surgical causes. The 48 patients spent an average of fifty-six days in the hospital, a total of two thousand six hundred and seventy-five days. The maximum number of days of hospitalization was two hundred and twenty-three; the minimum was one day, and the average per admission was thirty-four days. As the daily cost for hospitalization is $6.40, the average expense per patient for hospitalization was $358, a total of $17,120 for the 48 patients with esophageal strictures. This is a high penalty to pay for carelessness in leaving an everyday household article within the reach of curious children. Duke Hospital has had to bear the major part of the expense, as 85 per cent of the patients were unable to pay the minimum rate for hospitalization and required assistance from some welfare organization, Duke Hospital or the Duke endowment fund to finance the protracted treatment.

### PROGNOSIS

Trousseau's statement that "sooner or later all cases of esophageal stricture die of the bougie" has little basis today. All 9 of the patients for whom the Bokay therapy was adequate (table 3) escaped esophageal stricture, and the children were in good condition six months to four years after the accident. Strictures developed in 4 patients for whom the Bokay treatment was not continued at home and in 44 children who did not have Bokay treatment. Four of these 48 patients died, a mortality of 8 per cent. Two of the 4 patients died with esophagotracheal fistula, 1 with postoperative empyema and 1 with mediastinitis secondary to infection of the gastrostomy wound.

One of the patients had an esophagotracheal fistula at the time of admission to the hospital and died the same day. In the other patient the fistula developed because the esophagus, larynx and trachea had been burned severely; the child died after a long and stormy course. The patient who died as a result of operative injury had complete stenosis of the esophagus, and the latter was perforated in attempted dilation through the esophagoscope.

TABLE 3.—*Location of Strictures of the Esophagus Caused by Lye*

| Location | Number of Patients * | Percentage |
|---|---|---|
| Upper third | 16 | 43 |
| Middle third | 7 | 19 |
| Lower third | 7 | 19 |
| Upper and middle third | 1 | 3 |
| Upper and lower third | 2 | 5 |
| Middle and lower third | 4 | 11 |
| | 37 | |

* Five patients who required gastrostomy but for whom the location of the stricture is not known are not included in this table.

Malignant degeneration in the scar of a burn of the esophagus due to lye, mentioned by Vinson,[6] did not occur in any patient in this series.

## SUMMARY

Fifty-seven cases of ingestion of caustic alkali were analyzed.

Too many infants and children are poisoned with lye because it is carelessly left within their reach. The first aid given is generally poor because it is incomplete.

Patients with early poisoning due to lye can be saved the ordeal, expense and dangers of secondary stenosis of the esophagus by the use of Bokay prophylactic esophageal dilation. This treatment should be used for every patient who has swallowed alkali in any form, unless there is definite pharyngoscopic proof that the esophagus is undamaged. However, the treatment must be complete to be successful; too many patients are pronounced cured after receiving inadequate first aid.

Delay in treatment necessitates more drastic measures and is accompanied with 8 per cent mortality (as seen in this series), but careful attention to the prevention of secondary stricture and long-continued dilation produce good results in the other 92 per cent of the patients.

Duke University.

6. Vinson, P. P.: Cicatricial (Benign) Stricture of the Esophagus: Tabulated Report of One Hundred and Eighty-Six Cases, Ann. Otol., Rhin. & Laryng. **36**: 40-56 (March) 1927.

# STUDY OF THE PERSONALITIES OF CHILDREN WITH DIABETES

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The statement that children with diabetes mellitus are like other children in personality before the onset of the disease is made with caution, because it may be argued that diabetes is an endocrinopathy and that such a condition is often accompanied with disturbances of personality. However, so many children with diabetes remain normal that we can only say that the changes in others are the result of the disease itself. The abnormal personality that not infrequently develops with juvenile diabetes is worthy of discussion and investigation. Experiences in dealing with a large number of diabetic children for a few years in a summer camp conducted by the New York Diabetes Association were reviewed, and certain facts and common factors presented themselves.

During a recent summer camping period 114 children were seen, about an equal number of boys and girls, ranging in age from 6 to 18 years. The group was unselected except for the exclusion of children with contagious diseases or known delinquency. They were mainly children from greater New York, and most of them attended clinics in that city. A few were being cared for by private physicians. The group was representative of previous ones at the camp, and many of the children were "old campers."

About three fifths of the children maintained normality in all respects. Normality may be briefly defined as possession of a sense of security, acceptance by a group, interest in the activities of the group, a healthy attitude toward bodily functions without preoccupation by them, absence of the urgent need for indulgence at a given moment and ability to endure a moderate amount of deprivation. The data for normal children closely approximated those for children in the abnormal group. The groups were equally distributed as to sex. The average duration of the diabetic condition in the normal children (4.08 years) was similar to the average for the entire group (4.3 years) and to that for the children classified as abnormal (4.15 years). The average age of the normal children was 13.3 years, compared with 13 years for the whole group and 12.6 years for the abnormal children. The average age at the onset of diabetes for the normal children was 9.2 years, for the entire group 8.5 years and for the aberrant children 7.7 years. The normal and the abnormal group and the entire series included approximately the same percentages of children with excellent control of the diabetic condition, 53, 50 and 51 per cent respectively. Ketosis occurred frequently in 18 per cent of the children of the entire series and in only 12 per cent of those who were emotionally well adjusted, while the incidence in the abnormal children was 23 per cent, twice that in the normal children. From these data only two important facts stand out: First, in the children with abnormalities of personality the onset of diabetes occurred one and a half years earlier than in the children with normal personalities, and, second, twice as many of the children with abnormalities had frequent ketosis. Perhaps the first may be a cause of disorders of personality and the second a result.

That most children with diabetes appear to be normal is a credit to themselves, to their parents and to the clinic or doctor responsible for their supervision. The parents, and especially the mother, are subjected to the urgent need of the diabetic child for care, his excessive dependency and an intense conscious or unconscious desire for mothering. The parent who can respond to all of these and yet temper them with moderation and unobtrusiveness is an asset to the child. The child is indeed fortunate who is treated at a clinic or by a doctor who can control the diabetic condition without instilling ever present consciousness of calories and carbohydrates, of urinalyses and of injections of insulin.

About two fifths of the children observed at the camp were thought to be abnormal in one or more respects. The abnormalities ranged from true neurotic states to simple disturbances of personality. Such difficulties may be expected in persons with a chronic illness like diabetes. A child with diabetes is pitted against a force that does not yield. "Bringing the problem to consciousness," the time-worn remedy for a neurosis,

From the New York Diabetes Association, Inc.

* Resident Physician and Director, 1941 and 1942, Camp Nyda (summer camp for diabetic children, conducted by the New York Diabetes Association, Inc.).

does not help. The problems inherent in the diabetic condition remain, insoluble, incurable, and if the child cannot accept the actualities he is lost. A reaction of defeat and discouragement sets in, with a consequent sense of helplessness. At this point, if the parent suffers from the same sense of helplessness the die is doubly cast.

Comfort and avoidance of pain, two fundamental characteristics of the normal condition, are repeatedly denied the diabetic child. Every day he must recall that he cannot eat this or drink that; every day he must give himself insulin hypodermically. The normal ability to perform the excretory functions without preoccupation is also denied him. He must save specimens of urine; frequently he is made to time his voiding in relation to meals, and he is occasionally plagued by polyuria. One diabetic patient proudly announced that he could "guess" the percentage of sugar in his urine by its color at voiding! A diabetic adult on a cruise insisted that a fellow voyager come to his cabin for a display of his urine-testing equipment. The person with diabetes frequently forgets that no one else except another person with diabetes is interested in urinalysis.

The child who is different from his playfellows is a good candidate for a neurosis. A few children at the camp, even though among others with diabetes, were so unconditioned to group play that they frequently begged off from or interrupted games, theatrical performances or other juvenile activities with various somatic complaints. The complaints were of a nature usually heard only from adults with ingrained neuroses (for example, headache, backache, fatigue or palpitation).

A 10 year old boy at the camp for the first time presented the picture of an athletically active and normally aggressive child; he thought little of his diabetic condition, albeit it was always well controlled. After being subjected to the camp's elementary "lectures" on diabetes and routine urinalyses and to the other children's talk of diets, he became in the course of the following year increasingly more preoccupied with his disease; he began to question his mother's and his doctor's management and to suggest more frequent testing of urine. Instances like this have made us place less emphasis on diabetes at the camp and have made us decrease the number of urinalyses per day from four to two.

Aberrations of personality occurring in the young and adolescent children observed were of a few clearcut categories including the "aggressive," the "retiring," the "devil-may-care," the "immature," and the "escapist" type. All these disorders, of course, may result from the fact that diabetic children have a "feeling of difference."

Aggressive diabetic children may be like ordinary superior children who have to be best in games, best in school and best in health. This attitude is constructive. However, a few of these children become aggressive over unimportant things; they quarrel over minor events and give lectures to their fellows on scholastic topics or about matters that are common knowledge. One boy, who was really superior, memorized long poems and recited them breathlessly to any one who was polite enough to listen and held the impolite with the "ancient mariner's" grip. Another child, who was average, stated her belief in her superiority by saying that her father told her that Jewish children were brighter than others and that diabetic children were brighter than normal ones, leaving the evident conclusion to be made.

Retiring diabetic children are apt to be overshy and even mute. However, they do not seem to have the excessive sensitiveness and awareness so often associated with overshyness. One boy, seen in private practice, gave the impression of retardation until talked to away from his father, a dynamic business man who had taken over complete control of the boy's diabetic regimen. These children give the impression of "numbness."

The "devil-may-care" reaction is dangerous. Children who exhibit this reaction are characterized by overwhelming hopelessness; they generally eat anything and everything and eventually become escapists. An adolescent boy who wanted to obtain a pilot's license reacted with indifference when the danger of hypoglycemia was recalled to him. The boy had been completely out of control for four years and had deceived his parents and his doctor. He had failed to grow, and his height was 5 inches (13 cm.) less than the average for his age. His ordinary mode of conversation was one of untiring but pleasant flippancy. Another adolescent boy, who had frequent and severe episodes of ketosis, stated that he was given the syringe for his injection by his mother and sent into a closet room to administer it to himself; his mother could not bear the sight of the procedure. When he became "tired of it all," he ejected the insulin into the air and emerged from the room, triumphant in having deceived his mother and his doctor. This boy too was unvaryingly flippant.

The reactions of immature diabetic children are pleasant but infantile; at the age of 11 or 12 years they exhibit the judgments and reactions

of a child of 6 or 7 years. These children are frequently undersized and poorly controlled. Personality disorders of this type probably have an organic basis.

The escapist is the child who uses ketosis as a refuge from the unpleasantness of home or school or even as a refuge from the "struggle" against poorly managed diabetes itself. About one third of the children who had frequent episodes of ketosis came from homes broken by divorce, separation or widowhood, homes from which the mother was away all day and in which meals were consequently haphazard. Most of these children frankly stated that they liked the hospital better than home. The ordinary escapes of an unhappy child might be viewed as innocuous when compared with the devastating effects of the escape which is open to the unhappy diabetic child.

Normal adolescent children have many problems commensurate with their changing status. Diabetic adolescent children may be overwhelmed by their difficulties. They are subject to all the forms of adolescent flights of fancy, and inevitably they can satisfy but a few of them. They are thrown in with school fellows who make the cafeteria and the soda fountain their meeting place. If they do not become indulgent, they may become asocial. Undersized diabetic children may well feel inferior during this period in which rapid growth and maturation are normal. When they come to apply their maturing judgment to plans for a life work, they must do so with much more foresight than their normal contemporaries need to use. They must further bear in mind the hereditary possibilities of the disease, the life span associated with it and the complications now thought of as part of diabetes. It may be that at this age they begin to think that nature has played a monstrous physiologic trick on them. They may demand compensation for the handicaps, and this may result in a drive toward normality in all other respects or it may warp the personality.

Oddly enough, fear of the embarrassment and the danger of hypoglycemic reactions does not play a promient role in the makeup of young persons with diabetes. This may be because they have little or no memory of the episodes, due to the attendant physiologic decortication.

It is difficult to formulate rules for the prevention of disturbances of personality in young persons with diabetes. Each case must be handled individually, as in any other disorder, but a few simple guideposts stand out. With diet-insulin therapy for diabetes it is no longer necessary to make the child too conscious of food. The day of weighing food is over and measuring resembles the normal everyday way of dispensing food even in the home. The appreciation of only a few simple values for substitutions is all that is essential for successful dietary management. The problem of weaning from candy, ice cream and cake is a more difficult one; possession of these foods is almost the right of a child. The elimination should be sudden and complete, without recourse to substitutes. Self administration of insulin should be started in the hospital or the clinic and continued at home, even if the mother wants to assume the responsibility. When good control is attained, urinalyses should be less and less frequent, the management varying, of course, with the estimate of the child's dependability. Every urinary examination and the translation of the results into adjustment of the diet and the insulin therapy is a serious matter, and if the procedure is carried out incessantly it is prone to lead to irritability and even desperation. If urinalyses are distracting a child from normal pursuits or preoccupying him too much and yet are essential, let the mother become the tester. A mother may seek, with the best of intentions, to compensate her child for his illness by urging him too strongly in other pursuits. This, too, must be discouraged. Children who are too frequently in the hospital should be investigated for maladjustment. When children with diabetes are approaching adulthood they should be encouraged to discuss their problems and their future. If they seem unhappy, it does not really help to reassure them robustly that they are like any one else in adolescence. It may be a mistake to conclude that because modern therapy has made them physically indistinguishable from their neighbors diabetic persons are of the average emotional coloring. Finally, it may be advisable for the physician periodically to spend a half-hour in conversation with each child who has diabetes to find out how he feels about himself, his fellows and his environment. The patient's personality may be disclosed only then, even though he has made routine visits for control of diabetes for several months or years. The early recognition and treatment of emotional conflicts and behavioral disorders in children with diabetes by an alert physician might go a long way toward evolving better adjusted diabetic adults.

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# BASAL BLOOD PRESSURE AND PULSE RATE IN ADOLESCENTS

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Although measurements of the blood pressures of large populations of normal adults have been reported and the limits of normal variation have been fairly well established,[1] relatively few measurements have been made for developing adolescents.[2] Pulse rates of untold thousands of high school children have been counted under unknown conditions of rest or exercise, but the information available on changes in the basal pulse rate with age during the adolescent period is scanty.[3] This report presents the results of repeated measurements of pulse rate and blood pressure taken at intervals of six months for the same persons (children aged 11.5 to 17.5 years) under basal conditions over a period of six years.

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*Now Senior Psychophysiologist, United States Public Health Service, National Institute of Health, Unit on Gerontology, Bethesda, Md., and Visiting Physiologist, Baltimore City Hospitals, Baltimore.

1. (*a*) Medical Impairment Study (1929), New York, Actuarial Society of America, 1931. (*b*) Alvarez, W. C.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17-30 (July) 1923. Alvarez, W. C., and Stanley, L. L.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards, ibid. **46**:17-39 (July) 1930. (*c*) Hunter, R. G.: A Statistical Study of Blood Pressure, Am. Inst. Actuaries **13**:203 (Nov.) 1924. (*d*) Lewis, W. H.: Changes with Age in the Blood Pressures in Adult Man, Am. J. Physiol. **122**:491-505 (May) 1938. (*e*) Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409-444 (Sept.) 1939.

2. (*a*) Burlage, S. R.: The Blood Pressures and Heart Rate in Girls During Adolescence, Am. J. Physiol. **64**: 252-284 (April) 1923. (*b*) Faber, H. K., and James, C. A.: The Range and Distribution of Blood Pressures in Normal Children, Am. J. Dis. Child. **22**:7-28 (July) 1921. (*c*) Nylin, G.: The Physiology of the Circulation During Puberty, Acta med. Scandinav., 1935, supp. 69, pp. 1-77. (*d*) Richey, H. G.: The Blood Pressure in Boys and Girls Before and After Puberty, Am. J. Dis. Child. **42**:1281-1330 (Dec.) 1931. (*e*) Stocks, P., and Karn, M. N.: Blood Pressure in Early Life, in Studies in National Deterioration, Drapers' Company, Research Memoirs, 1924, vol. 11, pp. 1-88. (*f*) Sundal, A.: Normal Blood Pressure Curves in Age Groups of from 3 to 20 Years, Ztschr. f. Kinderh. **47**:742-761, 1929.

3. (*a*) Robinson, S.: Experimental Studies of Physical Fitness in Relation to Age, Arbeitsphysiol. **10**:251-323, 1938. (*b*) Sutliff, W. D., and Holt, E.: The Age Curve of Pulse Rate Under Basal Conditions, Arch. Int. Med. **35**:224-241 (Feb.) 1925.

## SUBJECTS AND PROCEDURE

The subjects for the cumulative study were 50 girl and 50 boys, chosen for the University of California Adolescent Growth Study from five elementary schools of Oakland, Calif. Since repeated testing of the same children was contemplated, selection of the subjects was based on the likelihood of their permanent residence and the cooperation shown by their parents. When first tested the children had a mean age of 11.87 years (with a standard deviation of 0.5 year).[4] The children of this group were retested at intervals of six months.

Additional groups of 50 girls and 50 boys were chosen from the same school population, and each child was given a single pair of tests. The boys were designated group A and the girls, group B. These children had a mean age of $16.0 \pm 0.2$ years at the time they were tested.

Similar tests were made for a group of 20 men who were medical students aged $23.9 \pm 0.7$ years[5] and 17 women students aged $23.2 \pm 0.7$ years. Values were also obtained for 20 men aged $32.5 \pm 0.3$ years and 17 women aged $33.4 \pm 1.2$ years.

On the morning of each test, the subject was brought by automobile to the laboratory, without breakfast. After the height and weight were measured, a standard 12.5 cm. cuff with leather backing was attached to the left arm. After determinations of blood pressure (by the use of a calibrated mercury manometer) and pulse rate were made with the subject in the standing position, he lay down on a cot for twenty minutes, during which time three additional measurements of pulse rate and blood pressure were made. Determinations of basal metabolic rate were then made by the open circuit method, for periods of eight minutes. Measurements of blood pressure and pulse rate were made at the close of each of three tests of basal metabolism. In the present report the average of the measurements taken at the end of the first and second tests of basal metabolism are presented.[6] The average of four measurements (two on each day) was computed for each subject and used in the present analysis.

4. A more detailed description of the children of this study is given by Jones (Jones, H. E.: The Adolescent Growth Study: I. Principles and Methods, J. Consult. Psychol. **3**:157-159, 1939; II. Procedures, ibid. **3**:177-180, 1939).

5. In this paper $\pm 1$ standard error is reported for all mean values.

6. The measurements made at the end of the third test were excluded because in many subjects these values were higher than the ones taken at the end of the second period. Ogden and Shock (Ogden, E., and Shock, N. W.: The Rate of Stabilization of Systolic Blood Pressure Following Adoption of the Supine Posture, Quart. J. Exper. Physiol. **28**:341-348 [Dec.] 1938) have shown that in adults twenty minutes' rest in the supine position affords ample time for stabilization of systolic blood pressure.

Pulse rates were counted for a full minute. Measurements of blood pressure were made by the auscultatory technic; systolic pressures were recorded at the first sound and diastolic pressures at the first muffling of the sound (fourth sound of Korotkow).

## RESULTS

*Reliability of Measurements.*—From the correlation between observations made at the end of the first and second tests of metabolism (about an minutes apart) it was found that the probable error of a single measurement of systolic blood pressure made under these conditions was 1.5 mm. for the values for boys and 1.8 mm. for the values for girls. The probable error of the values for diastolic pressures was 1.8 mm. for boys and 2 mm. for girls. The probable error of estimates of pulse rate was 1.8 beats per minute for boys and 2.5 for girls. The error of estimate of determinations of the blood pressure of adolescent children is thus of the same order of magnitude as that previously reported for determinations for adults.[7]

Correlations between measurements made on two successive days were also calculated and served to give an estimate of the day to day variability of blood pressure and pulse rate. The probable error of measurements on two successive days was calculated from the standard deviation of the distribution of the measurements and their correlation.[8] The probable error of measurement of the values for systolic blood pressure was 1.91 mm. for boys and 2.45 mm. for girls. For diastolic blood pressure the probable error of measurement was 2.2 mm. for boys and 2.5 mm. for girls. The probable error of measurement for pulse rate was 1.7 beats per minute for boys and 2.1 beats per minute for girls. Examination of the probable errors of measurement leads to the conclusion that fluctuations in basal pulse rate and blood pressure are almost as great during intervals of ten minutes as they are during periods of twenty-four hours.

*Age Norms for Blood Pressure and Pulse Rate.*—From the average of the four measurements made on two days distributions for each of the variables according to the ages of the subjects were prepared. Age classes were chosen so that the midpoints fell at years and half years. Because of unavoidable irregularities in the schedules of tests for some children the number of subjects in each age group varies between 50 and 30 except in the groups at 11.5 and 17.5 years, in which the number falls to 16. If two tests on the same child fell within the same age category, only the test nearest the midpoint of the category was used in the calculation. The results are summarized in the accompanying table.

*Table of Average Values for Basal Pulse Rate and Blood Pressure in Adolescent Children*

| Age, Years | Basal Pulse Rate, Beats per Min. | | | | Basal Blood Pressure, Mm. Hg | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Systolic | | | | Diastolic | | | | Pulse * | | | |
| | Boys | | Girls | | Boys | | Girls | | Boys | | Girls | | Boys | | Girls | |
| | Mean | σd† | Mean | σd | Mean | σd | Mean | σd | Mean | σd | Mean | σd | Mean | σd | Mean | σd |
| 11.5 | 67.5 | 6.6 | 74.1 | 11.7 | 102.7 | 6.7 | 106.6 | 9.6 | 68.7 | 5.3 | 72.9 | 6.5 | 34.7 | 5.3 | 34.1 | 7.5 |
| 12.0 | 69.5 | 8.1 | 71.4 | 7.8 | 104.2 | 7.2 | 103.8 | 7.3 | 71.1 | 5.2 | 71.3 | 6.9 | 33.8 | 4.8 | 33.7 | 5.1 |
| 12.5 | 66.8 | 6.6 | 69.2 | 6.0 | 104.9 | 6.7 | 105.9 | 7.0 | 69.8 | 4.8 | 71.6 | 7.2 | 35.4 | 5.9 | 34.8 | 5.3 |
| 13.0 | 65.9 | 6.0 | 67.8 | 8.0 | 106.0 | 6.1 | 105.3 | 7.0 | 69.6 | 5.2 | 69.8 | 5.2 | 37.1 | 5.4 | 36.3 | 5.4 |
| 13.5 | 66.2 | 5.5 | 69.6 | 8.1 | 107.7 | 6.7 | 107.5 | 7.9 | 69.0 | 5.8 | 68.3 | 6.1 | 39.3 | 6.1 | 39.1 | 6.9 |
| 14.0 | 67.1 | 7.0 | 68.3 | 6.9 | 110.7 | 6.6 | 108.0 | 7.0 | 68.5 | 4.8 | 68.0 | 5.3 | 42.8 | 6.3 | 40.6 | 6.5 |
| 14.5 | 66.0 | 6.1 | 67.6 | 6.9 | 110.7 | 6.6 | 106.4 | 4.6 | 68.3 | 5.1 | 67.0 | 4.8 | 43.3 | 5.1 | 40.1 | 5.4 |
| 15.0 | 65.2 | 5.5 | 67.3 | 8.6 | 110.4 | 7.0 | 105.4 | 6.7 | 69.3 | 4.8 | 68.3 | 5.4 | 42.1 | 6.5 | 38.4 | 5.5 |
| 15.5 | 63.1 | 6.4 | 66.7 | 8.2 | 111.1 | 6.2 | 104.1 | 5.4 | 70.3 | 5.1 | 68.1 | 5.1 | 41.5 | 6.2 | 36.9 | 5.2 |
| 16.0 | 61.6 | 6.5 | 65.8 | 7.6 | 112.4 | 7.1 | 106.8 | 9.3 | 71.3 | 5.5 | 69.4 | 5.4 | 41.7 | 6.8 | 37.5 | 6.7 |
| 16.0 ‡ | 61.5 | 7.9 | 66.7 | 8.3 | 113.3 | 10.0 | 104.3 | 4.8 | 72.0 | 6.9 | 75.8 | 7.5 | 42.0 | 7.1 | 37.2 | 4.0 |
| 16.5 | 60.8 | 6.3 | 66.4 | 8.4 | 111.1 | 7.0 | 104.9 | 4.8 | 70.3 | 4.9 | 67.8 | 5.9 | 41.2 | 5.5 | 37.9 | 6.5 |
| 17.0 | 58.6 | 4.8 | 64.1 | 6.9 | 114.7 | 7.0 | 107.0 | 8.0 | 71.9 | 5.1 | 69.1 | 7.8 | 43.4 | 6.8 | 38.6 | 6.7 |
| 17.5 | 58.7 | 6.8 | 63.7 | 6.3 | 114.4 | 6.3 | 105.4 | 6.4 | 71.0 | 4.6 | 68.7 | 4.5 | 43.8 | 5.8 | 37.1 | 5.6 |
| 24 § | 61.0 | 7.0 | 69.2 | 8.4 | 112.1 | 4.5 | 108.0 | 5.4 | 75.0 | 5.5 | 72.3 | 6.1 | 37.8 | 5.8 | 36.2 | 6.2 |
| 30 § | 59.3 | 6.1 | 64.8 | 8.5 | 114.4 | 6.9 | 110.0 | 5.1 | 80.0 | 7.0 | 75.8 | 7.5 | 34.8 | 4.4 | 34.8 | 5.0 |

* Pulse pressures were calculated from each individual set of measurements.
† σd represents the standard deviation of the distribution.
‡ Values for the control group of fifty 16 year old children who were tested only once.
§ Measurements for different groups of subjects.

Chart 1 shows the average pulse rates (beats per minute) of boys and girls between the ages of 11.5 and 17.5 years. The length of the vertical line through each point indicates the value for plus and minus one standard error of the mean. Points A and B indicate the mean values for the control groups of 16 year old boys and girls respectively. The values at the ages of 24 and 33 years were

7. Shock, N. W., and Ogden, E.: The Probable Error of Blood Pressure Measurements, Quart. J. Exper. Physiol. **29**:49-62 (March) 1939.

8. The formula used was $P.E._{r}=0.6745\frac{\sigma_1+\sigma_2}{2}\sqrt{1-r_{12}}$. Garrett, H. E.: Statistics in Psychology and Education, ed. 2, New York, Longmans, Green & Co., 1937.

obtained from measurement of different subjects, as described in a previous paragraph. Although the average pulse rate of girls is always greater than that of boys, the difference is not statistically significant.[9] However, the decrease in pulse rate during adolescence is statistically significant. In boys the average pulse rate falls from 69 beats per minute at age 12 to 59 at 17.5. In girls the decrease is from 72 to 64 beats per minute during the same period.

Chart 2 shows the average systolic blood pressures for adolescent boys and girls. There is no difference between the systolic blood pressures of boys and of girls under 3½ years of age. Between the ages of 11½ and 13½ the average blood pressure rises from 103 to 108 mm. in children of both sexes. After the age of

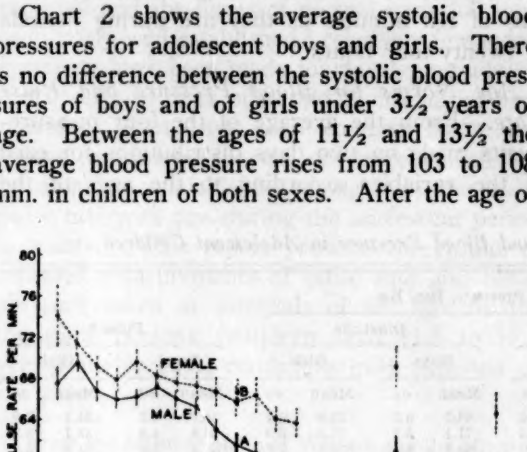


Chart 1.—Curves for average basal pulse rates of boys and girls tested every six months between the ages of 11.5 and 17.5 years. Connected points were obtained from tests on the same children as they matured. Points shown at ages 24 and 33 years were obtained from tests on other subjects (see text). Points marked *A* and *B* are average values for 50 additional boys and 50 additional girls aged 16 years who were tested for the first time at this age. The length of the vertical line through each point indicates the value of one standard error of the mean. The solid line represents the values for boys; the broken line, those for girls.

13½ the systolic pressure of boys continues to rise, reaching a value of 114 mm. when the boys are 17.5 years old, while that of girls drops slightly, reaching a minimum of 104 mm. when they are 15.5 years of age. In girls beyond this age there is a slight rise in pressure, to 106 mm. at 17.5 years. In this physiologic characteristic a sex difference develops during adolescence and seems to persist throughout life.

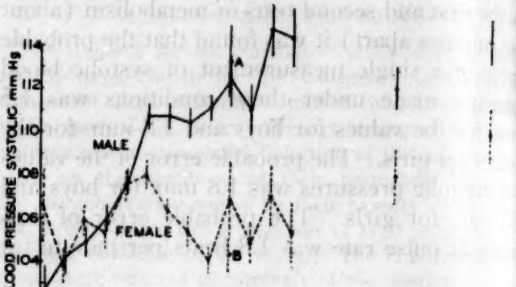


Chart 2.—Curves for average systolic blood pressures of boys and girls between the ages of 11.5 and 17.5 years and for men and women at 24 and 33 years.

Changes in the diastolic blood pressure with age are shown in chart 3. Between the ages of 12 and 14.5 years there is a downward trend in diastolic pressure of both boys and girls, but at 14.5 the average diastolic pressure begins to rise again, so that at 17.5 the values are almost the same as they were at 12 years. This rise in diastolic pressure seems to continue at least to age 35. There is no statistically significant difference between the diastolic pressures of boys and of girls during adolescence.

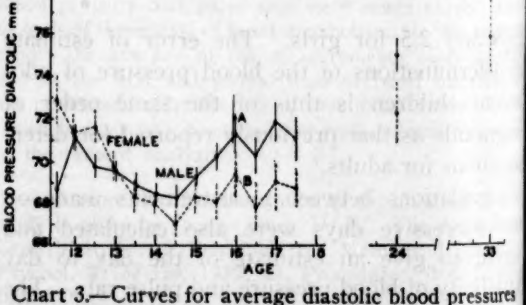


Chart 3.—Curves for average diastolic blood pressures of boys and girls between the ages of 11.5 and 17.5 years and for men at the age of 24 and women at the ages of 24 and 33.

Chart 4 shows the development of a sex difference in pulse pressure (systolic pressure minus diastolic pressure) in adolescent children. The average pulse pressure rises from 34 mm. at age 11.5 to 39 mm. at age 13.5 in both sexes. Beyond this age the pulse pressure of boys continues to rise, while that of girls falls, resulting in a sig-

9. The fact that the average pulse rate for girls is greater than that for boys at all ages cannot be used as an argument to establish the validity of the sex difference observed in this study, because, since the same children were measured at each age level, any chance sampling difference present at the first testing was maintained. However, different subjects were measured in the 24 and 33 year age groups; so the higher pulse rates for females than males offers some evidence of a true difference. Other investigators have also reported higher pulse rates for women than for men (Bowerman, W. G., and Brett, J. H.: Pulse Rates, Quart. Rev. Biol. **16**:90-99 [March] 1941; also footnotes 1 *a* and 3 *b*). Although pulse rate is negatively correlated with body size (Mautner, H.; Luisada, A., and Weisz, L.: Physiological Tachycardia in the Young, Arch. Pediat. **58**: 562-569 [Sept.] 1941), girls do not show slower pulse rates than boys between the ages of 11.5 and 14.5 years, when they are on the average taller and heavier than boys (chart 1).

nificant sex difference between the ages of 15 nd 17.5 years. It is interesting to note that his sex difference was not noted in adults tested nd that the values for pulse pressure were at preadolesecent levels.

*Effect of Early or Late Sexual Maturity on Basal Cardiovascular Measures.*—Inadequacies nd limitations of chronologic age as an index of naturity have long been recognized, but for linical use a successful substitute is yet to be levised. Other indexes of physiologic maturity ave been proposed, such as ossification of hand,

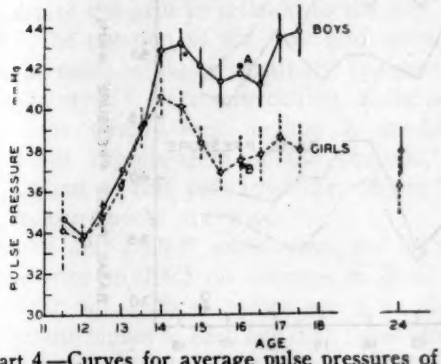


Chart 4.—Curves for average pulse pressures of boys nd girls between the ages of 11.5 and 17.5 years and or men and women at 24 years.

wrist, or knee,[10] menarche [11] or age of maximum ate of growth.[12] Of these age at menarche has erhaps been pursued with greatest enthusiasm. Although there is occasion for grave doubt of he advisability of basing estimates of maturity n a physiologic event subject to so many vari- ables both within and without the organism, it has been shown that in girls the rise in systolic blood pressure with age precedes menarche; after menarche there is no further systematic rise in systolic pressure during the adolescent period.[13]

Average values for girls who matured early and late as indicated by age at first menarche were calculated for each variable. Chart 5A shows the average blood pressures of 10 girls who matured early compared with the average blood pressures of 10 girls who matured later. In girls who matured early the systolic blood pressure was 2 to 8 mm. higher throughout adolescence than in girls who matured late. Chart 5B was constructed in the same manner and shows that during adolescence the pulse rate is 2 to 8 beats per minute slower in the girls who mature early than in those who mature late. Since maturity is characterized by slower pulse rate and higher blood pressure, it is apparent that girls who mature early sexually are usually advanced in maturity with respect to other physiologic variables.

Even if no other objections could be raised against using the age of menarche as a reference point to assess physiologic maturity, it is of limited value because it can be used only in girls. Since the age at which the adolescent spurt in growth reaches its maximum varies considerably

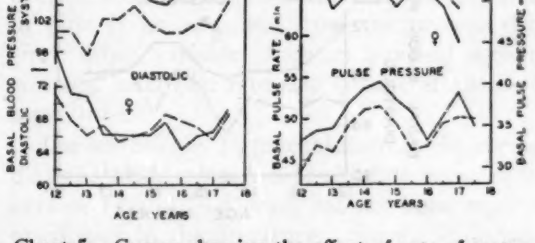


Chart 5.—Curves showing the effect of rate of maturing on basal blood pressure and pulse rate in girls. The groups were selected on the basis of age at menarche. The solid line represents the values for early maturing girls (mean age at menarche, 11.5 years); the broken line represents the values for late maturing girls (mean age at menarche, 14.75 years). Part *A* shows curves for the average basal systolic and diastolic blood pressures of early and late maturing groups, and part *B* shows similar curves for the basal pulse rates and pulse pressures.

in different persons, this characteristic may also be used as a rough index of physiologic maturity.[12] From measurements made at intervals of six months growth increments per tenth of a

10. (*a*) Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1936, vol. 1, no. 3, pp. 1-140. (*b*) Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

11. (*a*) Greulich, W. W.: Some Observations on the Growth and Development of Adolescent Children, J. Pediat. **19**:302-314 (Sept.) 1941. (*b*) Greulich, W. W.; Dorfman, R. I.; Catchpole, H. R.; Solomon, C. I., and Culotta, C. S.: Somatic and Endocrine Studies of Puberal and Adolescent Boys, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1942, vol. 7, no. 3 (serial no. 33), pp. 1-85. (*c*) Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, ibid., 1937, vol. 2, no. 5, pp. 1-252. (*d*) Shuttleworth, F. K.: Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen, ibid., 1938, vol. 3, no. 5, pp. 1-56.

12. Shuttleworth, F. K.: The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Age at Maximum Growth, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1939, vol. 4, no. 3, pp. 1-291.

13. Shock, N. W.: The Effect of Menarche on Basal Physiological Functions in Girls, Am. J. Physiol. **139**: 288-292 (June) 1943.

year were calculated for a number of physical measurements of each child. Since the most uniform pattern of adolescent development was evidenced by growth in stem length, this measurement [14] was used in the determination of the age of maximum rate of growth for each child, that is, in the determination of the midpoint of the period in which each child showed the maximum increment in stem length. For each sex the 10 subjects with the lowest age of maximum increment in stem length (early maturation) were compared with the 10 subjects with the highest age of maximum increment in stem length (late maturation) with respect to the cardiovascular measurements. Parts *A* and *B* of chart 6 show the curves obtained when girls are classified as having "early" or "late" maturation on the basis of the age at which they showed the adolescent spurt in growth. Parts *C* and *D* of this chart show similar data for boys. In both sexes the children who mature early have higher systolic blood pressures, higher pulse pressures and lower pulse rates throughout adolescence than children who mature later. These results offer additional evidence to support the view that in normal children the rate of growth and maturation is a general quality that finds expression in a variety of physical and physiologic areas.

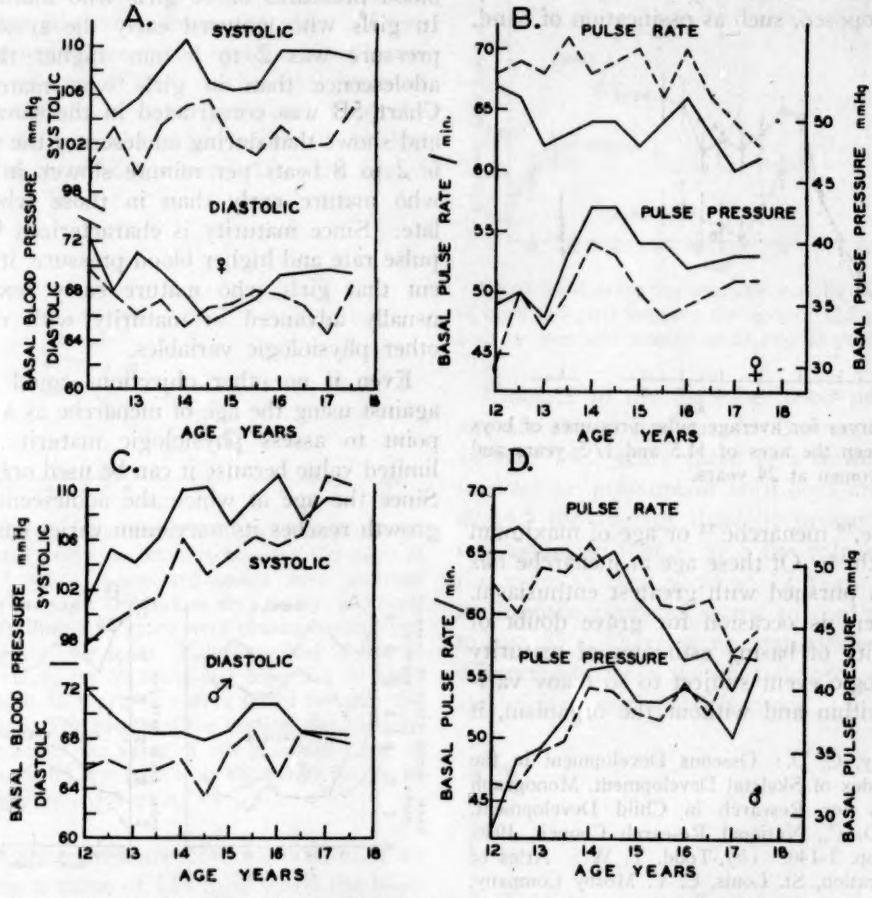


Chart 6.—Curves showing the effect of rate of maturing on basal blood pressure in girls and boys. The groups were selected on the basis of age at which maximum rate of growth in stem length occurred. *A* and *B* show the curves for girls. The solid lines represent the values for the early maturing group (mean age of maximum growth in stem length, 11.4 years); the broken lines, those for the late maturing group (mean age of maximum growth in stem length, 14.1 years). *C* and *D* show the curves for boys. The solid lines represent the values for the early maturing group (mean age of maximum growth in stem length, 13.5 years); the broken lines, those for the late maturing group (mean age of maximum growth in stem length, 16.0 years).

## COMMENT

Comparisons between the average values for pulse rate and blood pressure obtained in the

14. Stem length was measured from the top of the head to the buttocks when the child was seated with his sacral and scapular regions touching the vertical rule and with his feet resting on the seat, thus making the tuberosity of the ischium the lower limit of measurement rather than the tissue of the buttocks. This measurement is more reliable than that of sitting height. (Gray, H., and Ayres, J. G.: Growth in Private School Children, Chicago, University of Chicago Press, 1931.)

present study and similar values reported in the literature are of limited value because of differences in the technics of estimating blood pressures and in the conditions under which the determinations were made. Furthermore, the present study differs from others reported in the literature in that the same children were measured at each age, which tends to reduce the variability of the measurements. Many discrepancies between observations of blood pressure made by different investigators may be attributed to variations in the width of the cuff used,[15] the speed of compression and deflation of the cuff,[16] the size of the arm in relation to the size of the cuff,[17] the position of the arm and body,[18] the criteria used in the estimations (palpatory or auscultatory),[19] the interpretation of the sounds when the auscultatory method is used,[20] the degree of apprehension of the subjects,[21] and the amount of rest permitted the subject before the measurements are made.[6]

Sutliff and Holt [3b] summarized the data published prior to 1925 on changes in basal pulse rate with age. These values are 8 to 10 beats per minute higher at each age than those observed in the present study. Basal pulse rates of boys reported by Robinson [3a] are also higher. The lower pulse rates observed in the present study may be due in part to the greater size of the subjects at a given chronologic age, since there is a small negative correlation between body size and pulse rate.

The average systolic pressures reported by Richey [2d] for adolescents in Chicago are not significantly different from the values obtained in the present study; however, the average diastolic pressures reported for boys are 3 to 10 mm. lower. The diastolic pressures of girls beyond the age of 13 years reported in the two studies agree closely, but the averages reported by Richey for younger girls are 8 to 10 mm. lower than mine. Since attempts to reconcile these discrepancies must remain in the realm of conjecture, no further discussion seems warranted. The diastolic pressures observed in the present study do not differ significantly from those reported by Stocks and Karn [22] for boys and by Faber and James [2b] for children of both sexes.

The small difference between the pulse rates of boys and of girls which is apparently present even before sexual maturity may be contrasted with the definite difference between the systolic blood pressures which appears suddenly and develops rapidly after the children reach the age of 13.5 or 14.0 years. Although it has been recognized that blood pressure in normal boys and men is somewhat higher than in women and girls of the same age,[2f] the time at which the difference first appears has not been observed previously in adolescents. To attribute the difference in blood pressure to alterations in endocrine secretion which occur with the menarche in girls is unwarranted from the present data, since other variables such as physical activity, size and metabolic rate also change at about the same time.

The statistically significant decrease in average diastolic blood pressures of children between the ages of 12 and 14.5 years has not been reported previously in the literature. Since the decrease is about 4 mm. in the average curve, it is possible that observations made on different children at each age level would fail to show any consistent decrease.

My observations indicate that during adolescence there is a significant increase in pulse pressure in both boys and girls. Although the absolute magnitudes of pulse pressures reported by Stocks and Karn [22] are greater than those found by me, a similar rise of 8 to 10 mm. in pulse pressure was observed by them in British children. This rise in pulse pressure occurs at

15. (*a*) Day, R.: Blood Pressure Determination in Children: The Effect of the Width of the Cuff, J. Pediat. **14**:148-155 (Feb.) 1939. (*b*) Robinow, M.; Hamilton, W. F.; Woodbury, R. A., and Volpitto, P. P.: Accuracy of Clinical Determinations of Blood Pressure in Children, Am. J. Dis. Child. **58**:102-118 (July) 1939.

16. (*a*) Bazett, H. C.; Laplace, L. B., and Scott, J. C.: The Pressure Changes Induced in the Vascular System as the Result of Compression of a Limb, and Their Effect on the Indirect Measurement of Lateral Pressures, Am. J. Physiol. **112**:182-201 (May) 1935. (*b*) Wright, I. S.; Schneider, R. F., and Ungerleider, H. E.: Factors of Error in Blood Pressure Readings, Am. Heart J. **16**:469-476 (Oct.) 1938.

17. Ragan, C., and Bordley, E., III: The Accuracy of Clinical Measurements of Arterial Blood Pressure, with a Note on the Auscultatory Gap, Bull. Johns Hopkins Hosp. **69**:504-528 (Dec.) 1941.

18. Berry, M.: Influence of Position of Arm and Body on Blood Pressure Determined by Auscultation, Proc. Staff Meet., Mayo Clin. **16**:29-32 (Jan. 8) 1941.

19. (*a*) Groedel, F. M., and Miller, M.: Graphic Study of Auscultatory Blood Pressure Measurement, Exper. Med. & Surg. **1**:148-162 (May) 1943. (*b*) Kilgore, E. S.: Some Sources of Error in Blood Pressure Measurements, California State J. Med. **12**:97-102, 1914.

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the time of rapid growth of the thyroid gland.[22] Although neither Richey nor Faber and James observed this rise in pulse pressure during adolescence, I believe that it is characteristic of adolescent development.

## SUMMARY AND CONCLUSIONS

Determinations of pulse rate and blood pressure were made for a group of 50 adolescent boys and 50 adolescent girls under basal conditions. Duplicate determinations were made for the same children on each of two successive days every six months between the ages of 11.5 and 17.5 years. Pulse rates were counted for intervals of one minute, and blood pressures were read by the auscultatory method (first and fourth sounds as the criteria for systolic and diastolic pressures respectively) by the use of a 12.5 cm. cuff and a calibrated mercury manometer. Average curves of pulse rate and blood pressure (systolic, diastolic and pulse) were prepared on the basis of chronologic age, and the pulse rates and blood pressures of early and of late maturing children were compared. Analysis of the data showed the following:

1. Under basal conditions the probable error of measurement of systolic blood pressure is 1.5 mm. of mercury for boys and 1.8 mm. for girls. For diastolic pressure the probable error of measurement is 1.8 mm. for boys and 2.2 mm. for girls. The probable error of measurement of pulse rate is 1.8 beats per minute for boys and 2.5 beats per minute for girls. These values are not significantly different from those calculated from values for adults.

2. The average pulse rate for children decreases approximately 10 beats per minute between the ages of 11.5 and 17.5 years.

3. Systolic blood pressure in boys rises significantly during adolescence (from 103 mm. Hg at 11.5 years to 115 mm. at 17.5 years), but there is no significant change in systolic blood pressure in girls over the same age span. Beyond the age of 13.5 years boys have a greater systolic blood pressure than girls of the same age.

4. The average diastolic blood pressure reaches a minimum value in persons of both sexes at the age of 14.5 years and rises continuously thereafter.

5. During adolescence the average pulse pressure for both boys and girls rises 6 to 10 mm. Hg (maximum at age 14); it returns to the preadolescent level by the time the person is 24 years of age. The rise is more pronounced in boys than in girls.

6. Girls who mature early with respect to menstruation and children who experience the adolescent spurt in growth early are also more mature with respect to pulse rates and blood pressures.

Assistance in the preparation of these materials was furnished by the personnel of Work Projects Administration, O. P. 465-03-3-631, Unit A-8 and O. P. 65-1-08162, Unit A-8.

The staff of the Oakland Public Schools cooperated in making the subjects available for the study. During the course of the investigation Mrs. Olga Nave, Mr. Theodor Chernikoff, Miss Helen Brien, Mrs. Katherine Heck Long, Miss Pearl Bretnall, Mrs. Mary Alice Burmeister and Mrs. Elizabeth Replogle rendered valuable technical assistance.

Baltimore City Hospitals.

# EFFECTS OF REPEATED USE OF SULFADIAZINE FOR RECURRING ACUTE INFECTIONS OF THE RESPIRATORY TRACT

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That sulfonamide compounds have proved themselves of great value in the therapy of various infections no longer requires experimental or clinical brief. Nevertheless, their increasing popularity among physicians in general and the introduction of new derivatives have emphasized the necessity for clarifying at least two important problems bearing on the ultimate value of these drugs. On the one hand, the question has been raised whether the repeated administration of sulfonamide drugs in successive infections in the same patient may in some way lessen their therapeutic effectiveness. On the other hand, anxiety has been expressed not only that repeated application of the different derivatives might have a cumulative injurious effect on various organs and tissues but that it might even create in time a sensitized population unable to take the drugs safely. Evidences of sensitization have been frequently reported, and the manifold manifestations ascribed to this reaction include histologic changes in various organs characterized by disseminated focal necrosis and arteritis.[1] The nature of the mechanism participating in the changes is obscure, and a definite interrelation with allergy remains to be established. For the most part the data on sensitization are based on observations on selected patients in private practice and patients under treatment at hospitals and clinics. In the absence of adequate data on the effects of repeated use of the sulfonamide drugs, the relative frequency of sensitization is at present conjectural.[2]

It seemed of value in connection with studies under way on the control of acute infections of the respiratory tract[3] to determine what evidence could be furnished on the aforementioned problems, which have assumed increased importance with the widespread use of sulfonamide compounds. The clinical observations were made at Letchworth Village among feebleminded children of recognized high susceptibility to acute infections of the respiratory tract. All of the patients under observation were treated exclusively with sulfadiazine, and none had received this drug before the present study was undertaken. It was possible, therefore, to study a large group of persons previously untreated with the drug over approximately two years and thereby determine (1) the efficacy of sulfadiazine in repeated infections, (2) the cumulative toxicity of the drug and (3) the evolution of sensitization to

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From the Division of Infectious Diseases, the Public Health Research Institute of the City of New York.

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the drug. The selection of children for observation, the mental and physical characteristics of the children, their mode of living and the management of infections have all been described in earlier reports [3] and need not be repeated.

The children studied were 149 girls living in one cottage (cottage Y) and 192 boys living in another (cottage Iota). To approximately half of the children sulfadiazine was administered at the onset of symptoms of acute respiratory disease, and the remaining half did not receive any sulfonamide compound. In addition, two other sulfadiazine-treated groups were also observed, one consisting of 23 newly admitted inmates who received 0.75 Gm. of sulfadiazine daily during the first month of residence, and the other, of 30 children who were given 1 to 2 Gm. daily for fifteen weeks.[3d] With a daily maintenance dose of 2 Gm. the amount of free sulfadiazine per hundred cubic centimeters of blood usually varied from 4 to 10 mg.

## RESULTS

*Efficacy of Sulfadiazine in Repeated Infections of the Respiratory Tract.*—From Oct. 1, 1941 to June 30, 1943 sulfadiazine was given one or more times to 184 children in the treatment of numerous conditions, of which acute respiratory illnesses were most common. The distribution of these children by the number of courses of treatments received follows:

| Treatments * per Person | Number of Persons | Total Number of Treatments * |
|---|---|---|
| 1 | 85 | 85 |
| 2 | 33 | 66 |
| 3 | 23 | 69 |
| 4 | 17 | 68 |
| 5 | 9 | 45 |
| 6 | 7 | 42 |
| 7 to 16 | 10 | 97 |
| Total | 184 | 472 |

* A course of therapy lasting one or more days is considered as one treatment.

Of the 184 children treated, 99 (53 per cent) received sulfadiazine on two or more occasions. The duration of the courses of therapy (also referred to as "exposures" to the drug) varied from one to one hundred and five days, with a median of four days. The total amount of sulfadiazine received during each period of therapy ranged from 1 to 148 Gm., the median being 8 Gm. The interval between treatments varied from three days to ten months, with a median of three weeks.

In studying the effects of repeated applications of sulfadiazine on the course of the acute respiratory illnesses observed, the results of the treatment of the initial infection were compared with the results of the treatment of subsequent infections of the respiratory tract. The treatment of the initial respiratory infection during the period of observation represented the first exposure to sulfadiazine experienced by the child; the second treated infection, the second exposure to the drug, and so on. In comparing the courses of the various respiratory illnesses treated the following objective data were noted: maximum temperature on the first day of treatment, average duration of fever (rectal temperature above 100 F.), rise in temperature during the initial phases of the illness (primary rise) and subsequent rises in temperature (secondary rise). Excluded from the analysis that follows were the data for control children who became so ill as to require drug therapy and for all others who had had sulfadiazine at any time prior to their first treated respiratory illness during the period of the study. Two hundred

TABLE 1.—*Comparison of Clinical Data for First and for Subsequent Infections of the Repiratory Tract in the Same Persons, Treated with Sulfadiazine*

| Number of Illnesses per Person | Number of Persons | Order in Which Illnesses Occurred | Average Duration of Fever, Days | Frequency of Primary Rise in Temperature | | Frequency of Secondary Rise in Temperature | |
|---|---|---|---|---|---|---|---|
| | | | | No. of Illnesses | Per Cent | No. of Illnesses | Per Cent |
| 2 | 53 | First | 2.0 | 5 | 9.4 | 2 | 3.8 |
| | | Second | 2.1 | 7 | 13.2 | 5 | 9.4 |
| 3 | 29 | First | 2.4 | 3 | 10.3 | 2 | 6.9 |
| | | Second | 2.1 | 3 | 10.3 | 3 | 10.3 |
| | | Third | 1.9 | 3 | 10.3 | 2 | 6.9 |
| 4 | 17 | First | 2.5 | 2 | 11.8 | 2 | 11.8 |
| | | Second | 2.1 | 1 | 5.9 | 2 | 11.8 |
| | | Third | 1.6 | 2 | 11.8 | 1 | 5.9 |
| | | Fourth | 2.6 | 3 | 17.6 | 1 | 5.9 |
| 5 | 11 | First | 2.5 | 1 | 9.1 | 1 | 9.1 |
| | | Second | 1.7 | 0 | 0.0 | 1 | 9.1 |
| | | Third | 1.5 | 1 | 9.1 | 0 | 0.0 |
| | | Fourth | 2.6 | 0 | 0.0 | 1 | 9.1 |
| | | Fifth | 1.8 | 1 | 9.1 | 1 | 9.1 |

and seventy-six infections of the respiratory tract in 87 children satisfied these criteria and were therefore considered in the present study. Sulfadiazine was given for infections of the respiratory tract alone to 53 patients having 163 infections, while the remaining 34 children received the drug not only for infections of the respiratory tract but for other illnesses. All of the exposures to the drug were considered in determining the sequence of treatments.

A comparison of the data for the first and subsequent treated infections of the respiratory tract in the same children is given in table 1, in which the results obtained in the 53 children who received sulfadiazine in the treatment of infections of the respiratory tract only are summarized. Data were available for the first 2 infections in all of the 53 children, for the first 3 infections in 29, for the first 4 infections in 17 and for the first 5 infections in 11. The average duration

of fever did not vary significantly in any of these attacks. The temperature was consistently as high or higher during the first attack as during subsequent attacks. No significant differences were noted in the frequency of primary and secondary rises in temperature during the first attack and during subsequent ones.

The curves in chart 1 showing the average daily temperatures in the aforementioned infections are fairly closely superimposed, with little divergence from the mean. The differences are not considered significant. It is noteworthy that the average maximum temperature on the first day of illness was usually highest in the first infections. On the second and third days it was almost alike in all infections, and after the third day it again tended to be somewhat higher in the first infections than in the others. If the children were being sensitized or otherwise adversely affected by repeated exposures to the drug, one would expect the reverse to occur, that is, the maximum temperatures to be lowest in the first infections and highest in subsequent ones, particularly on the first day of treatment.

If the results for all the children considered in the study are combined, data are available on the effects of a fairly large number of primary and subsequent exposures to sulfadiazine in the treatment of infections of the respiratory tract. Summaries of these collective data are given in table 2 and chart 2. There was no significant difference in the average duration of fever in the first treated infection and in any of the others. The frequency of primary and secondary rises in temperature was somewhat lower in the first treated infection than in subsequent ones. However, the differences were not considered significant. In primary rises in temperature the maximum was usually reached on the second or third day and was usually below 102 F. Secondary rises in temperature almost always occurred between the third and the eighth day. In most instances the rise in temperature occurred during the course of drug therapy if this lasted for seven days or more; usually the temperature did not exceed 102 F. and the fever receded within forty-eight hours. The aforementioned changes in temperature were similar in character for the first and subsequent illnesses treated with sulfadiazine. They were also observed in the the control patients, in whom they not only occurred more frequenly but were more severe.[3] In some treated patients the infection appeared to be sufficiently pronounced to be responsible for the rise in temperature, but the possibility of a febrile reaction to the drug in others could not be excluded.

TABLE 2.—*Comparison of Collective Data for the First and for Subsequent Infections of the Respiratory Tract Treated with Sulfadiazine*

| Infection Treated | Number of Infections | Average Duration of Fever, Days | Frequency of Primary Rise in Temperature | | Frequency of Secondary Rise in Temperature | |
|---|---|---|---|---|---|---|
| | | | No. of Illnesses | Per Cent | No. of Illnesses | Per Cent |
| First | 87 | 2.1 | 5 | 5.7 | 5 | 5.7 |
| Second | 63 | 2.1 | 5 | 7.9 | 6 | 9.5 |
| Third | 41 | 1.9 | 5 | 12.2 | 5 | 12.2 |
| Fourth and fifth | 44 | 2.0 | 3 | 6.8 | 3 | 6.8 |
| Sixth to sixteenth | 41 | 1.9 | 4 | 9.8 | 5 | 12.2 |
| Total | 276 | 2.0 | 22 | 8.0 | 24 | 8.7 |

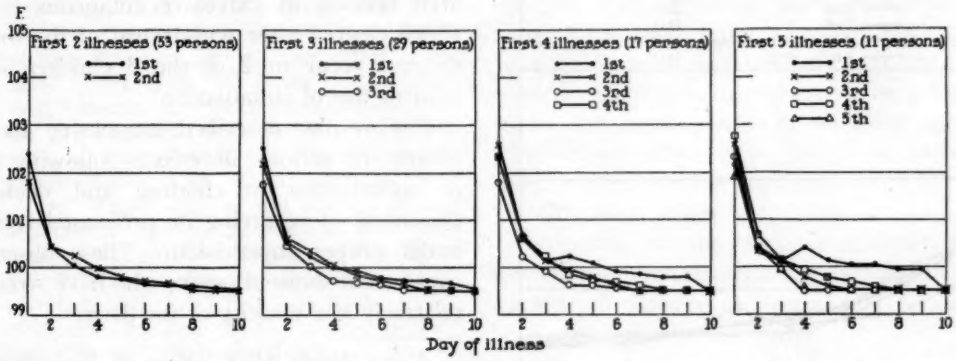


Chart 1.—Average daily temperatures in first and subsequent infections of the respiratory tract for all the persons considered in the study.

The average daily temperatures of the treated patients during the first and subsequent infections are graphically shown in chart 2. The temperature curve showed the same trend in each group of infections; there were a sharp drop on the second day of illness and a rapid return to normal limits. The fluctuations to either side of the mean were unrelated to the sequence in which the infections occurred. In general there was no delay in recovery following repeated application of the drug. For example, the curve for the last treated infections (sixth to sixteenth), which began at a somewhat higher level than

the mean, dropped below it on the second day and remained low for the remainder of the course. These changes were indicative of prompt recoveries such as were observed in the first treated infections.

*Toxic Reactions.*—Treatment was interrupted in 3 children because of an obvious intolerance for the drug. Each child had extensive maculopapular dermatitis, regional lymphadenopathy and fever that receded after the drug was withdrawn. In 2 children toxic symptoms occurred during the first course of therapy, in 1 on the fifth day and in the other on the fifteenth day. The first child had no toxic effects from sulfadiazine treatment for eight subsequent infections. The other child had a recurrence of symptoms on two other occasions, on the third day of the second treated illness and on the first day of the

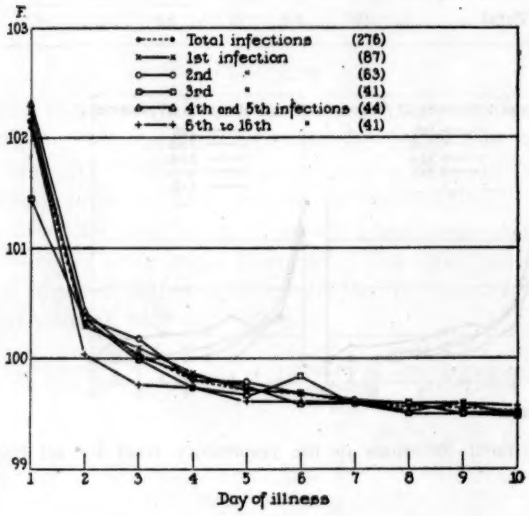


Chart 2.—Average daily temperatures in first and in subsequent infections of the respiratory tract in the same persons, treated with sulfadiazine.

third. There were no recognizable ill effects from three days' treatment of a fourth illness. The third child requiring interruption of treatment had a rash on the first day of the third treated illness. He had no discernible ill effects six weeks later during an illness that was treated for seven days.

No disturbing toxic effects were recognizable in any of the other children, even in those receiving the drug continuously for one hundred and five days.[3d] The children who were given sulfadiazine looked as well as the controls, and they maintained their general well-being. They showed no evidences of anemia, leukopenia or obvious impairment of renal function. Their average gain in weight was comparable to the gain observed among the controls.

According to the foregoing data obtained at Letchworth Village, there have been no serious ill effects from the repeated or prolonged oral administration of sulfadiazine in children and the course of recurring respiratory illnesses has not been adversely affected by past exposures to this drug.

## COMMENT

For almost two years sulfadiazine has been used repeatedly without serious mishap in the early treatment of acute respiratory illnesses among highly susceptible children at Letchworth Village, an institution for the feebleminded. Repeated or prolonged application of the drug did not seem to impair the general well-being of the children treated nor their response to infections of the respiratory tract prevalent at the time. In general, the average course of the first treated infection was similar to that of subsequent treated infections.

Treatment had to be interrupted for 3 children because of extensive cutaneous eruptions which cleared after withdrawal of the drug and did not recur in 2 of the 3 children on subsequent use of sulfadiazine.

The results described emphasize the infrequency of serious ill effects following the use of sulfadiazine in children and demonstrate the safety of recurring or prolonged treatments under proper supervision. These observations supplement those of others who have stressed the relatively low toxicity of the drug.[4]

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*(Footnote continued on next page)*

On the other hand, there have been an increasing number of case reports on the toxicity of sulfadiazine that clearly disclose its potential dangers. In addition to the cases previously cited,[3a, b] others have been reported. The toxic reactions reported include not only the formation of urinary concretions and renal damage [5] but extensive pemphigoid dermatitis, severe constitutional symptoms,[6] acute agranulocytosis,[7] acute hemolytic anemia,[8] acute thrombopenic purpura [9] and the developement of disseminated foci of necrosis in organs and blood vessels.[10] While some of the toxic effects ascribed to sulfadiazine may be coincidental changes etiologically unrelated to the drug,[11] others are undoubtedly caused by it. Even though the toxic effects of clinical importance are generally readily recognizable and usually recede after prompt withdrawal of the drug, the occasional deaths attributable to sulfadiazine [12] present a serious threat that confronts the practioner. Although indiscriminate application of the drug is admittedly unjustifiable, the excessive delay in treatment occasioned by timidity is also unwarranted and contributes to considerable suffering and an unknown number of deaths. Both extremes of attitude are reprehensible and accentuate the need for greater knowledge of the effects of the drug and wider dissemination of available information.

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## SUMMARY

In a study of the effects of repeated oral administration of sulfadiazine in the treatment of children with recurring acute infections of the respiratory tract from October 1941 through June 1943 the courses of the first and of the subsequent infections appeared to be comparable within the normal limits of sampling variability. The recognizable toxic effects of sulfadiazine were infrequent and were controlled by prompt withdrawal of the drug.

According to the experience described, the frequency of sensitization to sulfadiazine and of cumulative damage to organs and tissues must be considered of a low order.

Dr. Harry C. Storrs, Superintendent of Letchworth Village, aided in this work.

The sulfadiazine was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

Foot of East Fifteenth Street.

# Case Reports

## FETAL ERYTHROBLASTOSIS AND HABITUAL ABORTION

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The concept of erythroblastosis fetalis as a hemolytic familial disease entity has become firmly established. Ottenberg [1] was the first to suggest an antigen-antibody relationship between the red blood cells of the fetus and the blood of the mother. Macklin [2] observed that mothers of infants with erythroblastosis fetalis were subject to spontaneous abortions, miscarriages and stillbirths. Landsteiner and Wiener [3] demonstrated the Rh factor, an agglutinogen transmitted as a simple mendelian dominant characteristic and found in the red blood cells of 85 per cent of human beings. An erythroblastotic fetus inherits from the father the agglutinogen which determines the Rh positivity of the blood. Levine, Katzin and Burnham [4] and Levine, Burnham, Katzin, and Vogel [5] demonstrated the association of erythroblastosis fetalis with the Rh factor on the basis of isoimmunization. The modern concept is actually an application of the principles of isoimmunization laid down by Ehrlich and Morgenroth in 1900.[6] Rh agglutinogen from an infant with Rh-positive blood passes through the imperfect placental barrier into the blood of the mother. If the blood of the mother is Rh negative, anti-Rh agglutinins are produced in response to the Rh agglutinogen. They then pass through the placenta into the fetal blood, where they cause hemolysis of the fetal Rh-positive cells and produce the manifestations of fetal erythroblastosis.

### REPORT OF A CASE

The patient, a 34 year old white woman, was married for the first time in 1931, at the age of 23.

Between 1931 and 1934, she had two spontaneous abortions, one at two months, the other at three months.

In 1935 she became pregnant again and delivered an eight month, premature, severely jaundiced infant. A diagnosis of erythroblastosis fetalis was made; the child died in two days. An autopsy revealed a six week premature infant girl with jaundiced scleras and skin and a distended abdomen. There were small amounts of clear jaundiced fluid in the pleural, pericardial and peritoneal cavities. Microscopically, areas of hemopoietic tissue were found in the liver, pancreas, adrenal glands and lymph nodes. The sternal and tibial marrow was shown to be hyperplastic, with an increase in the erythroid elements. The blood showed severe erythroblastosis.

The patient was divorced in 1936. In 1938 she remarried. During the interval from 1938 to 1940 she had three pregnancies, in 1938, 1939 and 1940, all of which terminated in spontaneous abortions in the second and third month.

Still hoping for a viable child, the patient became pregnant once more in 1941. In view of the history of repeated abortions and the premature delivery of an erythroblastotic infant, tests for the Rh factor were performed on the blood of the patient and of her second husband.

The patient's blood was found to be Rh negative; her husband's, Rh positive. While these studies were in progress, the patient took a long train trip, shortly after which she spontaneously aborted a two month fetus.

At this time the patient's first husband was traced, and a sample of his blood was obtained for study. It proved to be Rh positive. In the interim he had remarried, and his second marriage was productive of a normal child.

The patient became pregnant again in 1942 but once more could not carry through. She spontaneously miscarried twins at six months' gestation.

### COMMENT

According to Diamond, Blackfan and Baty [7] erythroblastosis fetalis is manifested clinically by one of three predominant symptom complexes: icterus gravis neonatorum, universal edema of the newborn and congenital anemia of the newborn. The condition of the infant born to this patient in 1935 conformed classically to the icterus gravis neonatorum form of the disease.

The identification of the antigen-antibody combination evolved through the correlation of studies

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2. Macklin, M. T.: Erythroblastosis Foetalis, Am. J. Dis. Child. **53**:1245 (May) 1937.

3. Landsteiner, K., and Wiener, A. S.: An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223 (Jan.) 1940.

4. Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy, J. A. M. A. **116**:825 (March 1) 1941.

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6. Ehrlich, P., and Morgenroth, J.: Ueber Hemolysine, Berl. klin. Wchnschr. **37**:453, 1900.

7. Diamond, L. K.; Blackfan, K. D., and Baty, J.: Erythroblastosis Foetalis, J. Pediat. **1**:269 (Sept.) 1932.

of the reactions to intragroup transfusions in obstetric cases with studies of the blood of erythroblastotic infants and of their parents. In these studies it was shown that fetal erythroblastosis was due to an agglutinogen-agglutinin reaction and that the end result was hemolysis in the fetal blood. Isoimmunization explains the blood picture and the familial incidence of the disease.

The proportion of anti-Rh agglutinins in the mother's blood was found to diminish with the lapse of time after pregnancy, although in a few instances the agglutinins were present two months to a year or more post partum.

To quote Levine, Burnham, Katzin and Vogel,[5] "Since antibody production in general is characterized by a gradual rise, a period of maximum activity and gradual disappearance, it is conceivable that in some cases anti-Rh agglutinins, after exerting their lytic effect on the fetus, rapidly disappeared from the blood so that none could be demonstrated at the time of delivery."

From the above observation it is suggested that immune isoagglutinins reaching a peak of action early in the course of pregnancy produce either abortions or miscarriages. Those acting later may be responsible for erythroblastosis fetalis. Isoimmunization occurring near term may be responsible for relatively mild congenital anemia of the newborn infant. These factors might well have occurred in this patient as demonstrated by spontaneous abortions in the second and third months, miscarriage of twins in the sixth month and premature delivery of an eight month fetus with erythroblastosis fetalis.

Factors serving to limit the incidence of erythroblastosis fetalis may include individual resistance to any type of active immunization, impenetrability of the placental barrier, variation in the potencies and titers of the Rh factor and of the agglutinins thus produced and processes tending to inactivate the Rh factor in the maternal blood or the anti-Rh agglutinin in the fetal blood.

In the treatment of erythroblastosis fetalis transfusions play an important part. Only persons with Rh-negative blood should be used as donors, so that the cells may not be hemolyzed by any anti-Rh agglutinins remaining in the recipient's blood.

Mothers of erythroblastotic infants should not be permitted to nurse their children, since anti-Rh agglutinins may be transmitted in the mammary secretions.[8]

If artificial insemination is contemplated for the sake of viable children in mothers who have been denied them because of isoimmunization, it is necessary that the prospective sperm donor have Rh-negative blood. Cross matching between the blood of the donor and that of the recipient should be performed.

To carry the theoretic procedure a step further, if premarital tests for the Rh factor were practical, the occurrence of erythroblastosis fetalis could be foreseen and prevented. Certainly, however, every case of habitual abortion should be studied for the presence or absence of the Rh factor.

## SUMMARY

Habitual abortion and production of an infant with erythroblastosis fetalis occurred in a mother whose blood was Rh negative with two successive husbands, both of whom had Rh positive blood.

According to the present concept of the causation of the disease the fetus inherits the Rh factor from a father with Rh-positive blood. The Rh factor (agglutinogen) passes through an imperfect placental barrier into the Rh-negative blood of the mother. In response to the Rh agglutinogen, anti-Rh agglutinins are produced. These agglutinins pass through the placenta into the fetal blood, where they cause hemolysis of fetal red blood cells and produce the manifestations of erythroblastosis fetalis.

It is suggested that only Rh-negative blood should be used in the treatment of the disease and that mothers of erythroblastotic infants should not be permitted to nurse their children.

It is important to obtain a person with Rh-negative blood as a sperm donor if artificial insemination is contemplated for the mother of an erythroblastotic infant.

If premarital cross matching and tests for the Rh factor were performed the occurrence of erythroblastosis fetalis could be foreseen and prevented.

In all cases of habitual abortion tests for the Rh factor and its agglutinin should be made.

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8. (*a*) Witebsky, E.; Anderson, G., and Heide, A.: Demonstration of Rh Antibody in Breast Milk, Proc. Soc. Exper. Biol. & Med. **49**:179 (Feb.) 1942. (*b*) Witebsky, E., and Heide, A.: Further Investigations on the Presence of Rh Antibodies in Breast Milk, ibid. **52**:280 (April) 1943.

# FULMINANT MENINGOCOCCEMIA TREATED WITH PENICILLIN CALCIUM

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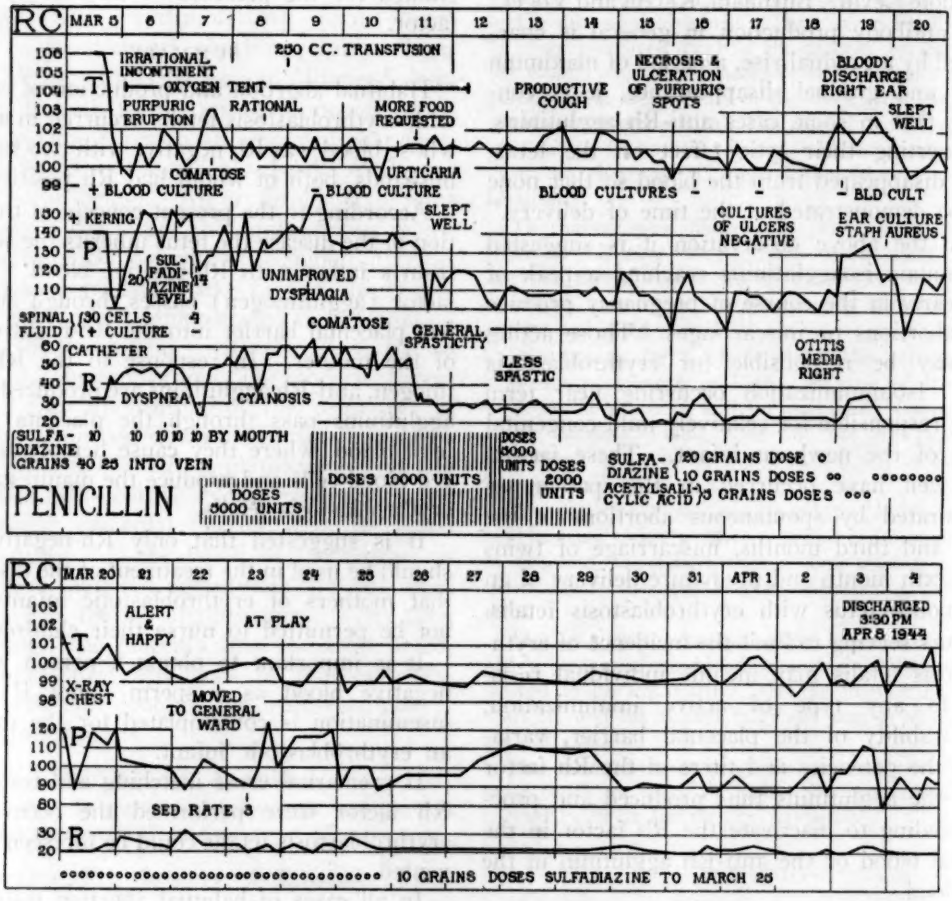
Martland [1] recently reported 19 fatal cases of the Waterhouse-Friderichsen syndrome, characterized by cyanosis, purpura, petechiae and bilateral gross hemorrhages in the adrenal glands, and by the presence of meningococci in the blood, without gross meningitis. Attempts to overcome the profound meningococcemia in 5 of the patients by intravenous injections of solutions of sulfadiazine and dextrose were futile and made no apparent impression on the course of the disease. Martland suggests that the usefulness of penicillin in the treatment of patients with fulminant meningococcemia is still a matter of conjecture.

We wish to report briefly regarding a boy of 8 years admitted to the hospital seemingly near death, with overwhelming meningococcemia, who was treated with sulfadiazine intravenously and by mouth for two days without result and then with penicillin intravenously and intramuscularly with complete success.




Abbreviated clinical record of R. C.

## REPORT OF A CASE

R. C., a white boy born Sept. 10, 1935, was admitted to the New York Post-Graduate Hospital on March 5, 1944. At birth he had weighed 5 pounds, 6 ounces (2,438 Gm.). He was not breast fed. His food had included vitamins. He had had whooping cough in 1936,

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1. Martland, H. S.: Fulminating Meningococcic Infection with Bilateral Massive Adrenal Hemorrhage (the Waterhouse-Friderichsen Syndrome), Arch. Path. **37**:147-158 (Feb.) 1944.

measles in 1938 and frequent colds, and a tonsillectomy was performed in 1938. Both parents were living and well. One brother, aged 15 years, had been mentally defective since birth.

On Feb. 26, 1944, the patient complained of dizziness and headache which persisted for two days. About March 3 a slight cold with running nose developed, and it persisted. However, on March 4 the patient engaged in his usual activities. On the evening of March 4 his temperature rose suddenly to 104 F. and he complained of pains in his legs and in the back of his head. Soon thereafter there were chills, projectile vomiting and delirium; ten hours after the observation of fever he was seen by a physician, who advised immediate hospitalization. He was carried into the hospital at 12 noon, March 5, 1944. At this time he was pale, cyanotic, irrational, with imperceptible pulse and with numerous petechiae over the body and extremities but not on the face. Respiration was shallow, with occasional dyspnea. A slight purulent nasal discharge was noted. The heart sounds were hardly audible, and the rate was extremely rapid, but no murmurs could be distinguished. The Babinski sign was positive on the right side and the Kernig and Brudzinski signs were positive on both sides. The diagnosis at the patient's admission was (1) meningococcic septicemia and (2) possible meningococcic meningitis.

Spinal fluid removed at about 12:10 p. m. contained a small amount of blood, and the few colonies of bacteria which appeared on culture plates inoculated with the spinal fluid may have come from the blood. A specimen of blood taken at the same time yielded an enormous number of colonies of meningococci in pure culture, many hundreds per millimeter of the patient's blood. At 12:10 p. m. intravenous infusion of 600 cc. of 2.5 per cent dextrose solution containing 40 grains (2.3 Gm.) of sulfadiazine sodium was started. The subsequent doses are indicated on the graphic chart. The patient was kept in an oxygen tent almost continuously. His condition remained desperate. On the morning of March 7 he became violently delirious and climbed over the side of his bed, but no apparent injury resulted. He was incontinent, restless and noisy and struggled and chewed at his restraining bandages. However, he did swallow fluids in small quantities.

At 11:57 a. m. on March 7 the first dose of penicillin was given intravenously, 5,000 units of the sodium salt in 5 cc. of isotonic solution of sodium chloride, and this amount was given again at 1:57 p. m. Soon thereafter a supply of the calcium salt[2] arrived, and this was used exclusively for the subsequent penicillin therapy indicated in the chart. On March 8 there was no evidence of improvement, and on March 9 there was progressive deterioration, increasing weakness, dyspnea, cyanosis and edema of the ankles. Endocarditis was considered certain, but even with acceptance of this diagnosis the lack of favorable response was disappointing. Respiration continued to be rapid even in the oxygen tent. Blood obtained at noon on March 9 remained culturally sterile. At that time the dose of penicillin was increased to 10,000 units every two hours.

2. The penicillin calcium was supplied by Chas. Pfizer & Company, 11 Bartlett Street, Brooklyn, in response to an urgent emergency appeal.

On March 11 there was dramatic improvement but with persistence of general spasticity. The pulse and respiration became much better, and oxygen therapy was discontinued on the morning of March 12. The dose of penicillin was reduced to 5,000 units the following midnight and to 2,000 units after the noon dose on March 13, and the administration was discontinued altogether the next afternoon (March 14). During the days of rapid improvement there was a productive cough; evidently there had been rather severe septic pneumonitis, which was now resolving.

Many of the purpuric spots on the skin became necrotic and sloughed, producing small deep ulcers. Material from several of the ulcers was cultured, but no organisms were demonstrated, suggesting that the meningococci originally concerned in their causation had been exterminated. All cultures of the blood, except the initial one of March 5, also remained sterile. Definite meningitis did not develop. However, there was inflammation of the right ear on March 18, with a bloody purulent discharge on the next day that yielded Staphylococcus aureus on culture. The patient was removed from isolation on March 22 and discharged in good condition on April 8.

The calcium salt of penicillin was given either intravenously or by intramuscular injection every two hours in doses of 5,000 units for two days and then in doses of 10,000 units every two hours for three and a half days more. There was mild urticaria on March 11, the fifth day of penicillin therapy, coincident with rapid general improvement of the patient's condition. We did not observe any other untoward effect which could be ascribed to the penicillin.

It is, of course, impossible to maintain that this boy would have died without penicillin. He was apparently moribund on admission, and the sulfadiazine seemed to prevent the impending death, though it appeared that death was merely being postponed by this agent. After the penicillin therapy was started, the issue of life and death remained in the balance for three days. Past experience with malignant fulminant meningococcemia has not inspired confidence in any therapy for this condition, and in the present instance the situation seemed hopeless from March 5 to March 10. The calcium salt of penicillin was evidently harmless, even in doses of 120,000 units per day, to a boy of 8 years, weighing about 60 pounds (about 27 Kg.).

## SUMMARY

A boy of 8 years recovered from fulminant meningococcemia after treatment first with sulfadiazine and subsequently with penicillin. The calcium salt of penicillin was found satisfactory and produced no serious untoward effects.

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# Progress in Pediatrics

## PRESENT STATUS OF THE RH FACTOR

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The manner in which laboratory experiments were correlated with clinical data and the importance of the Rh factor in relation to the causation of erythroblastosis and of certain reactions to intragroup transfusions was established is one of the most interesting stories in recent medical literature. The short time that has elapsed since the Rh factor was first described has been sufficient to permit numerous investigations, and over one hundred papers on various phases of this subject have already been published. In common with many new discoveries its importance may be currently overemphasized, and the ultimate place the Rh factor will take in medical thought and practice cannot yet be foretold. There are numerous problems still to be solved, but in the following pages an attempt will be made to summarize the available information that exists at present.

### HISTORICAL BACKGROUND

*Incompatible Blood as a Cause of Fetal and Maternal Morbidity.*—Some form of incompatibility between the mother and the fetus as a cause of morbid conditions in one or the other has been considered intermittently for many years. Dienst,[1] in 1905, was the first to note that when the mother's blood contained an $\alpha$ or $\beta$ agglutinin incompatible with the fetal cells the agglutinin titer of her serum was frequently higher four to eight days after delivery than it had been previously. He believed that the rise in titer resulted from the antigenic action of fetal cells that had gained entrance to the maternal circulation and that this increase in antibody titer was a cause of eclampsia. Murray (1910)[2] considered hemagglutinins and hemolysins from the fetus as a cause of maternal toxemia but dismissed the idea as improbable after learning that fetal isoagglutinins were frequently nonexistent at birth.

Somewhat later McQuarrie[3] found that the fetus and the mother were of incompatible blood groups in 70 per cent of 180 cases of toxemia. He thought that the normal placenta was inviolable, but he believed that occasionally a break occurred and fetal cells gained access to the maternal circulation. The thrombi present in some of the necrotic areas characteristic of livers of women with fatal eclampsia of pregnancy were believed to be clumps of fetal cells.

Gruhzit[4] in 1923 stated that while incompatibility between maternal and fetal blood existed in only 3 of 86 normal pregnancies it was uniformly present in 16 cases of eclampsia or preeclampsia. He concluded that a specific agglutinable substance from the fetal erythrocytes passes to the mother's system as a fetal waste product and in the mother's blood stream is agglutinated and suspended in fine colloidal particles; the presence of a colloidal substance produces an increase in the viscosity of the blood, which in turn causes the symptoms of toxemia. Gruhzit also suggested[5] that incompatibility of blood groups might be responsible in some cases for idiopathic sterility and miscarriage.

About the same time Ottenberg[6] discussed the findings of Dienst and McQuarrie and concurred in the belief that eclampsia was most often due to immunization of the mother by the continuous introduction of small numbers of incompatible fetal cells into her blood. In the last paragraph of his paper he suggested that jaundice of the newborn and certain types of hemorrhagic disease might be due to accidental placental transfusion of incompatible blood. This seems to mean that he believed maternal cells could enter the fetal circulation and reverse the process thought to initiate eclampsia.

That the agglutinin titer of maternal serum rises during pregnancy if the fetal blood is of a group incompatible with that of the mother and that the incidence of incompatibility is greater

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2. Murray, H. L.: The Haemotoxic Nature of Eclampsia, with an Account of the Foetal and Placental Hemolysins and an Experimental Investigation into the Anaphylactic Theory of Eclampsia, J. Obst. & Gynaec. Brit. Emp. **18**:225, 1910.

3. McQuarrie, I.: Isoagglutination in Newborn Infants and Their Mothers, Bull. Johns Hopkins Hosp. **34**:51, 1923.

4. Gruhzit, O. M.: Toxemias of Pregnancy from a New Aspect, Am. J. Obst. & Gynec. **5**:400, 1923.

5. Gruhzit, O. M.: Eclampsia—Is It a Biological Necessity? Am. J. Obst. & Gynec. **7**:588, 1924.

6. Ottenberg, R.: The Etiology of Eclampsia, J. A. M. A. **81**:295 (July 28) 1923.

in toxemic than in nontoxemic patients was denied by Allen [7] in 1926 after studying 104 toxic and 375 nontoxic patients. He found that in approximately 21 per cent of both groups of patients the mothers and infants were of incompatible blood groups and that the average agglutinin titer was 1:79 for toxic as well as for nontoxic patients.

The possibility that differences in blood groups might be responsible for erythroblastosis was mentioned by Hirszfeld [8] in 1928 and Paroli [9] in the same year reported that among 27 women who had had abortions only 1 was of the same blood group as her husband. Jonsson [10] in 1936 again confirmed the statement that the titer of anti-A or anti-B agglutinins in maternal serum rises appreciably when the cells of the fetus are incompatible with those of the mother.

In 1938 Darrow [11] reviewed the literature on erythroblastosis and from an analysis of the published data concluded that the best explanation for erythroblastosis lay in an antigen-antibody reaction. She made no mention of differences in the AB antigens present in the blood of the mother and of the fetus as a cause of the antigenic reaction but postulated a difference in the chemical components of fetal and of adult hemoglobin which would make possible a maternal sensitization to the fetal type. Darrow thought that the disease could be produced in the fetus by the transmission of maternal antibodies through the placenta and in the infant after birth by the ingestion of antibodies in breast milk. Her reasoning was logical, and her theory of the causation of erythroblastosis explained many of the conditions associated with this disease. Some support for this theory was subsequently obtained when she and her collaborators [12] produced antiserums in rabbits that differentiated fetal from adult hemoglobin.

*Reactions to Intragroup Transfusions.*—Prior to the establishment by Landsteiner [13] in 1900 of the group-specific character of human erythrocytes, intravenous administration of blood had not been practicable because of the severe reactions that followed its introduction into the circulation. After the four major groups were discovered [14] and a simple method for their determination was established,[15] it was possible to give transfusions with relative impunity. Continued investigation revealed the presence of subdivisions in groups A and AB in 1911 [16] and in 1927 [17] additionally recognized individual properties of human blood were designated M, N and P. Other irregular agglutinins have been demonstrated,[18] the majority of which were more active at 0 C. than at 20 C. or 37 C. These are known as cold agglutinins because of their greater activity at low temperatures, and they often agglutinate the person's own cells as well as those of others in the same blood group. They appear to be of practically no significance as far as reactions to transfusions are concerned.

Landsteiner and Levine in 1929 [19] and 1930,[20] while studying blood from 500 patients, found a high percentage of cold agglutinins and observed that the action of 3 per cent of these agglutinins persisted at room temperature. Five of the patients received transfusions of blood the cells of which were agglutinated at 20 C. by the recipient's serum. No reactions followed. This observation is of special interest in relation to the present belief that blood showing such agglutination should never be administered.

A few hemolytic reactions were known to occur, however, that could not be explained by the presence of any known agglutinin. In reviewing the literature available by 1940 it is evident that these reactions occurred largely in pregnant or previously pregnant women [21] or in persons who had previously been given transfusions.[22] Wiener

7. Allen, W. M.: Interagglutination of Maternal and Fetal Blood in the Late Toxemias of Pregnancy, Bull. Johns Hopkins Hosp. **38**:217, 1926.

8. Hirszfeld, L.: Konstitutionsserologie und Blutgruppenforschung, Berlin, Julius Springer, 1928.

9. Paroli, G.: La disarmonia constituzionale paterno-materna quale elemento patogenetico di aborto, Riv. ital. di ginec. **7**:388, 1928.

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11. Darrow, R. R.: Icterus Gravis (Erythroblastosis) Neonatorum, Arch. Path. **25**:378 (March) 1938.

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13. Landsteiner, K.: Zur Kenntnis der autifermentativen, lytischen, und agglutinierenden Wirkungen des Blutserums, und der Lymphe, Zentralbl. f. Bakt. (Abt. 1) **27**:357, 1900.

14. (*a*) Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr. **14**:1132, 1901. (*b*) von Decastello, A., and Sturli, A.: Ueber die Isoagglutinine in Serum gesunder und kranker Menschen, München. med. Wchnschr. **49**: 1090, 1902.

15. Hektoen, L.: Isoagglutination of Human Corpuscles, J. A. M. A. **48**:1739 (May 25) 1907.

16. von Dungern, E., and Hirschfeld: Ueber gruppenspezifische Strukturen des Blutes, Ztschr. f. Immunitätsforsch. u. exper. Therap. **8**:526, 1911.

17. Landsteiner, K., and Levine, P.: On Individual Differences in Human Blood, J. Exper. Med. **47**:757, 1928.

18. Landsteiner, K., and Levine, P.: On the Cold Agglutinins in Human Serum, J. Immunol. **12**:441, 1926.

19. Landsteiner, K., and Levine, P.: On Isoagglutinins Reactions of Human Blood Other Than Those Defining the Blood Groups, J. Immunol. **17**:1, 1929.

20. Landsteiner, K., and Levine, P.: On the Inheritance and Racial Distribution of Agglutinable Properties of Human Blood, J. Immunol. **18**:87, 1930.

*(Footnotes continued on next page)*

and Peters [23] called attention to this fact at that time.

Stetson [21a] in 1933 reported the extremely interesting history of a young woman who had had 5 normal children. After an induced abortion at two months she had been given five transfusions. The first, from a brother, was uneventful; the second, from a professional donor, was also uneventful, but the donor's cells were later shown to be agglutinated by the patient's serum. The third transfusion was from the husband and was followed by a severe reaction; the fourth and fifth transfusions, from 2 of the patient's brothers, were also uneventful. This case caused much speculation on the part of the author as to why the early transfusions were satisfactory, why the cells of members of the family were all compatible and why the husband's blood should have caused such a severe reaction. He concluded that an inherited latent isoagglutinin might be present in several members of the family and that introduction of foreign blood might stimulate the development of agglutinin to a point where the titer would be sufficiently high to cause agglutination of all cells from persons outside of the family. The author wished to attempt to induce the formation of the antibody in one of the patient's brothers but was refused. Had the brother cooperated, successful immunization might well have been accomplished. In view of our present knowledge the reaction exhibited by this patient seems to have been a definite example of immunization to the Rh factor.

Culbertson and Ratcliffe [21b] in 1936 described 2 patients whose serum agglutinated the cells of many members of the same blood group. They commented on the fact that the mother of 1 patient was the only person whose cells the patient's serum did not agglutinate. They also noted that both patients had recently been pregnant and stated: "Although we attach no significance to the fact, it should be noted that in both cases the intragroup agglutinin was demonstrated during the puerperium."

Parr and Krischner [21c] and Goldring and Graef [21d] each reported reactions to transfusions of husband's blood to a patient with hemorrhage following an abortion. Both patients recovered.

However, not until 1939, when Levine and Stetson [22d] reported "an unusual case of intragroup agglutination," was the suggestion made that pregnancy might be specifically related to the presence of atypical intragroup agglutinins. These authors observed a woman whose serum agglutinated the cells of 80 per cent of all persons in the same blood group and suggested that she might have become immunized to some agent that the fetus had inherited from the father. The fetus had been harbored in a nonliving state for six weeks before it was delivered.

The stage was thus set for the developments which were to follow in rapid succession. It had been shown that when atypical agglutinins capable of causing a reaction at transfusion were present (1) the patient had either previously had transfusions or recently been pregnant, (2) if the patient had recently been pregnant the pregnancy had often terminated with abortion or intrauterine death of the fetus, (3) blood cells of the patient's siblings or parents were often the only ones not agglutinated by the patient's serum and (4) transfusion of the husband's blood was frequently responsible for a reaction. The suggestion had been made that the fetus, because of its inheritance from the father of an antigen

21. (*a*) Stetson, R. E.: Causes and Prevention of Posttransfusion Reactions, S. Clin. North America **13**: 319, 1933. (*b*) Culbertson, C. G., and Ratcliffe, A. W.: Reaction Following Intra-Group Blood Transfusion: Irregular Agglutinin Demonstrated by the Sensitive Centrifuge Test Method, Am. J. M. Sc. **192**:471, 1936. (*c*) Parr, L. W., and Krischner, H.: Hemolytic Transfusion Fatality with Donor and Recipient in Same Blood Group, J. A. M. A. **98**:47 (Jan. 2) 1932. (*d*) Goldring, W., and Graef, I.: Nephrosis with Uremia Following Transfusion with Incompatible Blood, Arch. Int. Med. **58**:825 (Nov.) 1936. (*e*) Johnson, R. A., and Conway, J. F.: Urinary Suppression and Uremia Following Transfusion of Blood, Am. J. Obst. & Gynec. **26**:255, 1933. (*f*) Von Deesten, H. T., and Cosgrove, S. A.: Renal Insufficiency Following Blood Transfusion: Recovery After Venesection, Ann. Int. Med. **7**:105, 1933. (*g*) Smith, C. E., and Haman, J. O.: Reaction Following Blood Transfusion, California & West. Med. **41**: 157, 1934. (*h*) Zacho, A.: "Unverträglichkeit" zwischen Blutproben vom gleichen Bluttypus, beruhend auf dem Vorhandensein eines irregulären Agglutinins gegenüber einem bisher unbekannten Rezeptor, Ztschr. f. Rassenphysiol. **8**:1, 1936. (*i*) Pondman, A.: Difficulties in Blood Group Determination, Nederl. tijdschr. v. geneesk. **82**:6111, 1938; cited by Wiener and Peters.[23] (*j*) Mandelbaum, H. M.: Hemolytic Reactions Following Blood Transfusion: Report of a Case of Intra-Group Incompatibility, Ann. Int. Med. **12**:1699, 1939. (*k*) Bernstein, A.: Anuria Following Blood Transfusion, Am. J. Obst. & Gynec. **39**:1045, 1940. (*l*) Hamilton, E. G., and Martini, A. P.: Blood Transfusion in Pregnancy: A Review of Three Thousand Cases, ibid. **43**:313, 1942.

22. (*a*) Neter, E.: Observations on Abnormal Antibodies Following Transfusions, J. Immunol. **30**:255, 1936. (*b*) DeGowin, E. L., and Baldridge, C. W.: Fatal Anuria Following Blood Transfusions: Inadequacy of Present Tests for Compatibility, Am. J. M. Sc. **188**:555, 1934. (*c*) Baron, C.: The Present Status of Hemolysis in Blood Transfusions with Report of a Fatal Case, Kentucky M. J. **30**:326, 1932. (*d*) Levine, P., and Stetson, R.: Unusual Case of Intra-Group Agglutination, J. A. M. A. **113**:126 (July 8) 1939.

23. Wiener, A. S., and Peters, H. R.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group with Three Cases in Which the Same Agglutinogen Was Responsible, Ann. Int. Med. **13**:2306, 1940.

lacking in the mother, might be the source of the factor producing an immune state in the mother.

*Discovery of the Rh Factor and Establishment of its Clinical Significance.*—It had been known for some time that certain substances and the blood of certain animals when injected into test animals produced antibodies capable of reacting with blood cells other than those inciting their production. In 1937 Landsteiner and Wiener [24] produced anti-M agglutinins in rabbits by the injection of blood from the rhesus monkey Macaca mulatta. Following this line of investigation they [25] later obtained an antirhesus serum which after absorption to remove antibodies characteristic of the species still contained an agglutinin (unrelated to any previously described) that agglutinated the cells of 39 of 45 human bloods. The agglutinogen thus identified was designated Rh because of its presence in the cells of the rhesus monkey. Human cells that were agglutinated by the antirhesus (anti-Rh) serum were designated as Rh positive (Rh +), and those not agglutinated, as Rh negative (Rh —).

Shortly thereafter Wiener and Peters [23] observed 3 patients who had had severe reactions after receiving transfusions of homologous blood. The action of antibodies found in the blood of these patients paralleled that of the anti-Rh agglutinins. It was concluded that in these patients the production of antibodies had been stimulated by the previous administration of Rh-positive blood and that the subsequent introduction of similar cells resulted in agglutination and hemolysis.

Later in 1940 Levine and his co-workers [26] observed that the serums of several patients who had had repeated miscarriages or abortions contained atypical isoagglutinins related to the Rh factor, and in 1941 Katzin found that the serum of the patient previously described by Levine and Stetson [22d] agglutinated the same cells as the newly discovered anti-Rh rabbit serum. Had it been possible to retest the patients previously described by Zacho, Neter, Stetson, Culbertson and Ratcliffe and others, they also could probably have been shown to possess an agglutinin identical with or related to the antirhesus agglutinin. Additional papers published within a short time by Levine and Polayes,[27] Wiener [28] and Scott and Conant [29] gave further support to the belief that Rh-positive blood introduced by transfusion or from the placenta could produce immunization.

Soon after the realization that a specific antibody was present in certain patients who had had a high incidence of unsuccessful pregnancies, Levine, Katzin and Burnham [30] thought it significant that a diagnosis of erythroblastosis had been made on some of the dead fetuses. In further investigations on the blood of other women who had had infants with this disease they and Vogel [31] found that the majority of the mothers had Rh-negative blood, in contrast to the high percentage of women in the general population whose blood was Rh-positive. In a paper by Burnham [32] and in two editorials by Levine [33] that appeared during 1941 further attention was called to the relationship of the Rh factor to erythroblastosis, and the theory of an immunologic basis for erythroblastosis became fairly well established. It was shown that erythroblastosis and possibly other conditions affecting the fetus or the newly born infant were the result of an antigen-antibody reaction: Rh-positive fetal cells entering the maternal blood were believed to stimulate the formation of anti-Rh agglutinins; maternal agglutinins passing

24. Landsteiner, K., and Wiener, A. S.: On the Presence of M Agglutinogens in the Blood of Monkeys, J. Immunol. **33**:19, 1937.

25. Landsteiner, K., and Wiener, A. S.: An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223, 1940.

26. (*a*) Levine, P., and Katzin, E. M.: Isoimmunization in Pregnancy and the Varieties of Isoagglutinins Observed, Proc. Soc. Exper. Biol. & Med. **45**:343, 1940. (*b*) Levine, P.; Katzin, E. M., and Burnham, L.: Atypical Warm Isoagglutinins, ibid. **45**:346, 1940.

27. Levine, P., and Polayes, S. H.: An Atypical Hemolysin in Pregnancy, Ann. Int. Med. **14**:1903, 1941.

28. Wiener, A. S.: Hemolytic Reactions Following Transfusions of Blood of Homologous Group: Further Observations on the Role of Property Rh, Particularly in Cases Without Demonstrable Isoantibodies, Arch. Path. **32**:227 (Aug.) 1941.

29. Scott, J. E., and Conant, J. S.: Successful Transfusions Following Previous Hemolytic Transfusion Reaction Due to Rh and Anti-Rh Factors: Report of Case, Am. J. Clin. Path. **11**:536, 1941.

30. Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy: Its Possible Bearing on the Etiology of Erythroblastosis Foetalis, J. A. M. A. **116**:825 (March 1) 1941.

31. (*a*) Levine, P.; Vogel, P.; Katzin, E., and Burnham, L.: Pathogenesis of Erythroblastosis Fetalis: Statistical Evidence, Science **94**:371, 1941. (*b*) Levine, P.; Burnham, L.; Katzin, E., and Vogel, P.: The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**:925, 1941.

32. Burnham, L.: Common Etiology of Erythroblastosis and Transfusion Accidents in Pregnancy, Am. J. Obst. & Gynec. **42**:389, 1941.

33. (*a*) Levine, P.: The Role of Iso-Immunization in Transfusion Accidents in Pregnancy and in Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**:165, 1941. (*b*) Levine, P.: The Role of Iso-Immunization in Transfusion Accidents and in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Clin. Path. **11**:898, 1941.

back to the fetus then agglutinated and destroyed the fetal erythrocytes.

By this time it was evident that the Rh factor in human cells was of definite clinical significance in its relationship to reactions to intragroup transfusions and to erythroblastosis. For the first time it became possible (by using Rh-negative blood) to give transfusions safely to the majority of the patients who had previously had reactions to intragroup transfusions. The fact that pregnancy could stimulate immunization and make possible a reaction to a first transfusion was also realized.

The large volume of work performed by subsequent investigators has almost without exception corroborated the fundamental concepts of Levine, Wiener and their associates.

### PRESENT STATUS OF THE RH FACTOR

*The Rh Antigen.*—The Rh factor is an antigen present on the surface or within the substance of some human erythrocytes. Wiener [34] has suggested that it lies partially beneath the surface in contrast to the more superficially located A, B, M and N.[35] It was originally thought to be present only in erythrocytes,[36] but subsequently it was found in liver, kidney, spleen and salivary gland.[37] It is absent from or present in only extremely small amounts in body fluids. It appears early in fetal life and has been demonstrated in a fetus of 17 cm. by Bornstein and Israel.[38] Koucky [39] has demonstrated anti-Rh agglutinins in the mother during the twelfth week of pregnancy, and in the older literature [40] there are several accounts of reactions to intragroup transfusions given for hemorrhages resulting from tubal pregnancies. The previous obstetric history is not recorded in any of these cases, and it is possible that the production of agglutinins had first occurred in a previous pregnancy; if this is true, it need not necessarily indicate that the Rh antigen was present in the cells of the embryo prior to the time the presence of agglutinins was first demonstrated.

The antigenic potency appears high in some instances, although there is great individual variation. Levine [41] stated that 90 per cent of all accidents in intragroup transfusions are due to the Rh factor. Although this may be true, relatively few cases have been reported in which symptoms can be attributed to the antigenic action of this substance (table 7). The smallness of the number may be due partly to lack of investigation or partly to the assignment of reactions to complicating conditions instead of to hemolysis.[42] However, several fairly extensive reports [43] covering many thousand transfusions show few reactions which could possibly be due to immunization to the Rh factor. With the establishment of blood banks and the consequent greater availability of blood, more patients may receive multiple transfusions and the number of reactions may increase.

It is probable that red blood cells must be intact in order to exert an antigenic effect, although Kariher [44] has stated the belief that the molecular components of fragmented cells may retain their antigenic capacity. At the present time there is no experimental support for this contention. The cells, as far as is known, must be introduced directly into the circulating blood before they can act as antigens, although to date there has been no formal report of attempted immunization by intramuscular, subcutaneous or other routes. The two ways in which the antigen

34. Wiener, A. S., cited by Hooker, S. B.: Isoimmunization in Relation to Intragroup Hemolytic Transfusion Reactions, New England J. Med. **225**:871, 1941.

35. However, Wiener, Sonn and Belkin (The Nature of the Rh Agglutination Reaction, Science, to be published), from recent observations, suggest that the explanation of the peculiarities of the Rh reaction is that there are far fewer Rh haptens than A and B haptens per red blood cell.

36. (*a*) Wiener, A. S., and Forer, S.: A Human Serum Containing Four Distinct Isoagglutinins, Proc. Soc. Exper. Biol. & Med. **47**:215, 1941. (*b*) Levine, P., and Katzin, E. M.: Pathogenesis of Erythroblastosis Fetalis: Absence of the Rh Factor from Saliva, ibid. **48**:126, 1941.

37. Boorman, K. E., and Dodd, B. E.: The Group-Specific Substances A, B, M, N and Rh: Their Occurrance in Tissues and Body Fluids, J. Path. & Bact. **55**:329, 1943.

38. Bornstein, S., and Israel, M.: Agglutinogens in Fetal Erythrocytes, Proc. Soc. Exper. Biol. & Med. **49**:718, 1942.

39. Koucky, R. W.: Experiences with the Rh Substance in Transfusion Reactions, Minnesota Med. **26**: 980, 1943.

40. Bordley, J.: Reactions Following Transfusion of Blood with Urinary Suppression and Uremia, Arch. Int. Med. **47**:288 (Feb.) 1931.

41. Levine, P.: The Pathogenesis of Erythroblastosis Fetalis and Related Conditions, Cincinnati J. Med. **23**: 596, 1943.

42. Wiener, A. S.: Hemolytic Transfusion Reactions: Diagnosis with Special Reference to the Method of Differential Agglutination, Am. J. Clin. Path. **12**:189, 1942.

43. (*a*) Erf, L. A., and Jones, H. W.: Experiences Associated with a Transfusion Unit in a 700 Bed Hospital: An Animal Survey of Over 3,500 Administrations of Blood and Plasma (Dried), Ann. Int. Med. **19**:1, 1943. (*b*) Mollison, P. L.: The Investigation of Haemolytic Transfusion Reactions, Brit. M. J. **1**: 529 and 559, 1943. (*c*) Wiener, A. S.; Oremland, B. H.; Hyman, M. A., and Samwick, A. A.: Transfusion Reactions: Experiences with More Than 3,000 Blood Transfusions, Am. J. Clin. Path. **11**:102, 1941.

44. Kariher, D. H.: Erythroblastosis Fetalis (Hemolytic Disease of the Newborn) Occurring in One of Two Twins, J. A. M. A. **122**:943 (July 31) 1943.

is ordinarily introduced into a foreign host are by blood transfusion and by the passage of fetal blood into the maternal circulation from the vessels in the placental villi.

*Anti-Rh Agglutinins.*—Antibodies formed in response to the Rh antigen act as agglutinins in vitro and as hemolysins within the body. Wiener and Peters [23] stated that even though serum was freshly activated by the addition of complement no hemolysis could be obtained in vitro. This is surprising in view of the fact that hemolysis is practically always preceded by agglutination [45] and that an easily performed laboratory experiment consists in agglutinating erythrocytes with appropriate serums and subsequently hemolyzing them by the addition of complement. Koucky [39] postulated the production of several types of Rh antibodies, including agglutinins, hemolysins, precipitins, cytotoxins and others; none have been demonstrated except the agglutinin-hemolysin.

Anti-Rh agglutinins are not normally present in the human body, and when demonstrated they have been, with one possible exception,[46] passively transmitted or have resulted from the antigenic action of artificially introduced cells. Antibodies against Rh-positive cells cannot develop in a person with Rh-positive blood, and Rh antibodies are never present in such persons except in those rare instances in which an infant with Rh-positive blood has agglutinins transferred to it through the placenta.[47] Free Rh-positive cells may be found in the circulation of a person with Rh-negative blood after the transfusion of Rh-positive blood; because of this phenomenon a person with Rh-negative blood may be incorrectly classified as having Rh-positive blood immediately after transfusion.

When Rh-positive cells enter the circulation of a person with Rh-negative blood, antibodies against the Rh-positive cells may be formed. The response depends on the antigenic potency of the cells introduced and the ability of the recipient to produce immune bodies. Some cells are poor in antigenic quality and some persons are poor reactors to antigenic stimuli; under such conditions no immunization occurs. On the other hand, if both factors in the antigen-antibody reaction are high immunization may develop rapidly.

The amount of blood and the number of injections necessary to cause production of antibodies have not been definitely established and are probably subject to considerable variation. In women who have never been pregnant and in men, at least two transfusions have preceded practically all the reactions for which it seems probable that anti-Rh agglutinins were responsible; usually there have been many more preceding transfusions. Dacie and Mollison,[48] however, have reported finding anti-Rh agglutinins in Rh-negative blood after a single transfusion. The patient had had one pregnancy; the child had Rh-negative blood. In 7 patients who had received multiple transfusions studied by Koucky,[39] antibodies developed within four to thirty-three days after the first transfusion. The patients had been given 500 to 2,200 cc. of blood. The shortest interval for immunization was exhibited by a patient who was four months pregnant, in whom a reaction developed on the fourth day, with the third transfusion. In 10 nonpregnant patients observed by Vogel, Rosenthal and Levine,[49] reactions occurred twenty-one days to twenty months after the first transfusion. Most of the patients had had many intervening transfusions.

Up to the present time many more accidents due to transfusions following pregnancy than following previous transfusions have been reported. Immunization produced by pregnancy gives a higher and more sustained titer of anti-Rh agglutinins than that produced by transfusion alone [46]; it is probable that the frequent introduction of small amounts of blood from the placenta initiates a greater response than does the introduction by transfusion of larger amounts of blood at greater intervals.

Levine [50] recently reported obtaining agglutinins in rabbits after fourteen daily injections of 2 cc. of a 1:5,000 suspension of human blood. This, he stated, would be equivalent to the administration of 0.0672 cc. of red blood cell sediment to a 120 pound (54.5 Kg.) woman, and he concluded that since the placental villi have such a great surface area it is probable that immunizing doses of red blood cells escape into the maternal circulation during all pregnancies. If this were true, the only women with Rh-negative blood who would escape immunization

45. (*a*) Moss, W. L.: Studies on Isoagglutinins and Isohemolysins, Bull. Johns Hopkins Hosp. **21**:63, 1910. (*b*) Irsigler, F. J.: Urämie nach Bluttransfusion, Zentrabl. f. Chir. **58**:1682, 1931.

46. Diamond, L. K.: Hemolytic Transfusion Reactions Due to the Rh Factor: A Preventable Danger, New England J. Med. **227**:857, 1942.

47. (*a*) Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: Clinical Significance of the Rh Factor, Brit. M. J. 2:535 and 569, 1942. (*b*) Diamond, L. K.: Personal communication to the author.

48. Dacie, J. V., and Mollison, P. L.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Hemolytic Anemia, Lancet **1**:550, 1943.

49. Vogel, P.; Rosenthal, N., and Levine, P.: Hemolytic Reactions as a Result of Isoimmunization Following Repeated Transfusions of Homologous Blood, Am. J. Clin. Path. **13**:1, 1943.

50. Levine, P.: The Pathogenesis of Erythroblastosis Fetalis: A Review, J. Pediat. **23**:656, 1943.

by a fetus with Rh-positive blood would be those incapable of forming antibodies against the fetal cells.

The concentration of agglutinins in the blood is rarely high, and commonly the titer is only 1 : 4 or 1 : 8. One of the highest titers recorded [39] was 1 : 5,000, present six days after the termination of pregnancy. The comparison of titers obtained by different laboratories is difficult because of the great variation in the agglutinability of the cells used in the determination of the titer. Erythrocytes exhibiting strong agglutinability may give a titer several times greater than that obtained by the use of weakly reacting cells.

Agglutinins may not be demonstrable by any laboratory method and yet may make their presence known by producing reactions to transfusions or erythroblastosis. They may, on the other hand, become demonstrable at any time after a transfusion or during pregnancy; if they are associated with pregnancy, they may show a progressive rise as long as the fetus is within the uterine cavity. Occasionally the titer continues to rise for a few days after the birth of an infant with erythroblastosis, and at times agglutinins which were nondemonstrable during pregnancy and the immediate postpartum period may be present one to two weeks later. Boorman, Dodd and Mollison [47a] were able to demonstrate agglutinins seven to twenty-one days after delivery more commonly than at any other time.

Subsequent to the assault which originally produces the agglutinins or which stimulates their further production, the titer usually falls and agglutinins may be nondemonstrable within a few months. They may, however, persist for many years; Race, Taylor, Cappell and McFarlane [51] reported finding agglutinins eight years after the last gestation, and Newton and Tebbutt [52] observed a reaction from a first transfusion fourteen years after the last preceding pregnancy.

The concentration of agglutinins has little relation to their persistence; the serum, mentioned by Koucky,[39] which soon after delivery had a titer of 1 : 5,000 is stated to have contained no agglutinins three months later.

Agglutinins may be temporarily absent after the introduction of Rh-positive blood because all circulating antibodies have united with the newly introduced Rh-positive cells. Wiener [28] called this a negative phase. Subsequent examinations, three to five days later, will usually again reveal agglutinins in the circulation.

When antibodies cannot be demonstrated (except immediately after a transfusion), it is believed that they are held in the reticuloendothelial system or some other part of the body ready to be released by appropriate stimulation.

Antibodies in general appear capable of passing through the normal placenta. This ability has been best demonstrated in relation to the passage of diphtheria antitoxin [53] and syphilitic reagins.[54] Anti-Rh agglutinins likewise pass through the placenta and enter the body of the fetus. In most instances they seem to be removed from the circulation rapidly, but Boorman, Dodd and Mollison [47a] were able to demonstrate anti-Rh agglutinins in the blood of a pair of Rh-positive twins, both of whom died of erythroblastosis soon after delivery, and Diamond [47b] observed anti-Rh agglutinins in several infants within a short time after birth.

Many antibodies are known to pass through the breast into the colostrum and milk. The presence of Rh antibodies in breast milk was demonstrated in 3 cases by Witebsky, Anderson and Heide [55] and in 2 cases by Potter and Davidsohn.[56] Although little is known of the action of gastric juices on antibodies, it may be possible that agglutinins derived from breast milk are at times the cause of progressive neonatal anemia.

*Relation to Sex and to other Antigenic Substances in Blood.*—The presence of the Rh factor is entirely unrelated to sex or to the existence of any other known character of human blood.[57] Agglutinins against Rh, like those against M and N, are never normally present (anti-N agglutinins have never been observed, and anti-M

51. Race, R. R.; Taylor, G. L.; Cappell, D. F., and McFarlane, M. N.: The Rh Factor and Erythroblastosis Foetalis: An Investigation of Fifty Families, Brit. M. J. **2**:289, 1943.

52. Newton, N. C., and Tebbutt, A. H.: A Fatal Blood Transfusion Reaction Apparently Due to the Rh Factor, M. J. Australia **2**:109, 1943.

53. (*a*) Ruh, H. O., and McClelland, J. E.: Comparison of Diphtheria Immunity in the Mother and in the New-born, Am. J. Dis. Child. **25**:59 (Jan.) 1923. (*b*) Rothholz, A., and Kuttner, A. G.: Comparison of the Schick and the Dick Test in Mothers and Newborn Infants, ibid. **47**:559 (March) 1934. (*c*) Cooke, J. V., and Sharma, B. M.: Schick Test in the Newly Born, ibid. **44**:40 (July) 1932.

54. Wiener, A. S., and Silverman, I. J.: Permeability of the Human Placenta to Antibodies, J. Exper. Med. **71**:21, 1940.

55. (*a*) Witebsky, E.; Anderson, G. W., and Heide, A.: Demonstration of Rh Antibody in Breast Milk, Proc. Soc. Exper. Biol. & Med. **49**:179, 1942. (*b*) Witebsky, E., and Heide, A.: Further Investigations on the Presence of Rh Antibodies in Breast Milk, ibid. **52**:280, 1943.

56. Potter, E. L., and Davidsohn, I.: Unpublished data.

57. Landsteiner, K., and Wiener, A. S.: Studies on an Agglutinogen (Rh) in Human Blood Reacting with Anti-Rhesus Sera and Human Isoantibodies, J. Exper. Med. **74**:309, 1941.

agglutinins have been recorded only five times),[58] but, unlike M and N, Rh is definitely antigenic. It is unlike A and B, since the appropriate isoagglutinins against A and B are normally present in all persons who lack one or both of these characters. Normal isoagglutinins against the Rh factor have never been reported, with the possible exception of 1 case in which the patient was a 5 year old child.[46] Unlike A and B but like M and N the Rh antigen is present in saliva in only extremely small amounts. All of the antigens mentioned (A, B, M, N and Rh) appear to be present in liver, kidney and salivary gland.[37]

*Subgroups of the Rh Agglutinin and Agglutinogen.*—The Rh factor is not a single uniform antigen that is constant in its action. In early studies it became evident that some variation existed. Anti-Rh agglutinins present in the serums of different persons gave fairly uniform reactions with the majority of blood cells, but with a few they gave reactions which were dissimilar both qualitatively and quantitatively.

Wiener has been more active than any other investigator in an attempt to group the types of blood into specific categories according to their responses to the anti-Rh agglutinins present in various human and animal serums. It is interesting to note the increasing complexity of his nomenclature as more and more variability has been discovered. Early in his work studies were described [57] in which not all cells gave a uniform response to all serums being used. When the first serum that gave positive reactions with only 70 per cent of the samples of blood was encountered, he stated that the antibody demonstrated in case 4 of his series was not the standard Rh agglutinin but an Rh-like antibody.[28] Slightly later, in a study of the American Indians, a similar serum is spoken of as demonstrating "a variant of Rh." [59] On the basis of these observations Wiener soon came to the conclusion [60] "that there are at least two sorts of Rh agglutinogen, analogous, for example, to the two major varieties of A agglutinogen, $A_1$ and $A_2$. It is evident that the special anti-Rh serum tentatively may be compared in its behavior to the anti-$A_1$ serum which can be prepared by absorbing B serum with $A_2$ cells. Accordingly, bloods agglutinated by this special anti-$Rh_1$ serum as well as the standard anti-Rh serum, can be designated as $Rh_1$, while bloods agglutinated only by standard anti-Rh sera are designated as $Rh_2$. As has already been pointed out, about 85 per cent of all white individuals are Rh-positive, and of these approximately one-sixth belong to subtype $Rh_2$." He also stated in the same paper, "Levine has shown that by absorbing certain anti-Rh sera with $Rh_2$ blood, a reagent can be obtained which gives reactions parallel to anti-$Rh_1$ sera." Wiener finally decided that an almost complete analogy existed between the types of the Rh factor and those of the A factor.

Levine [61] about the same time (1942) reported that he, Landsteiner and Wiener had agreed on terminology. The serum which agglutinated cells from 85 per cent of the population was called anti-$Rh_1$, and that agglutinating cells from 73 per cent, anti-$Rh_2$. A third serum, which agglutinated 87 per cent of all blood, was designated anti-$Rh_{1,2}$ because it was believed to have antibodies of two types, whereas $Rh_1$ and $Rh_2$ each had antibodies of a single type.

Wiener [62] early in 1943 used this system of nomenclature, though by that time he had concluded that the Rh factor was much more complicated in its behavior than agglutinogen A and that the resemblance was only superficial. He stated that from studies of distribution of the Rh factor it seemed necessary to postulate the existence of three qualitatively different agglutinogens instead of only two, one reacting with anti-$Rh_1$ serum but not with anti-$Rh_2$, a second reacting with anti-$Rh_2$, but not with anti-$Rh_1$, and a third reacting with both anti-$Rh_1$ and anti-$Rh_2$ serums.

Later in the same year he and Landsteiner [63] in another paper declared that "in place of the nomenclature suggested by one of the writers,[62] the following less complicated designations are now suggested. When a distinction between the various subtypes of Rh is desired, the great majority of bloods, namely, those which react also with serum no. 2 of the table (anti-$Rh_1$ serum), are designated as $Rh_1$. Of these, a small percentage fail to react with guinea pig antisera or human sera listed as No. 1 and are designated as $Rh_1$. Those bloods which do not react with sera anti-$Rh_1$ (No. 2) are called $Rh_2$. The agglutinins are named so as to correspond to agglutinogens of the blood cells."

58. Davidsohn, I., and Toharsky, B.: The Rh Blood Factor: An Antigenic Analysis. Am. J. Clin. Path. **12**:434, 1942.

59. Landsteiner, K.; Wiener, A. S., and Matson, G. A.: Distribution of the Rh Factor in American Indians, J. Exper. Med. **76**:73, 1942.

60. Wiener, A. S.: Hemolytic Transfusion Reactions: III. Prevention with Special Reference to the Rh and Cross-Match Tests, Am. J. Clin. Path. **12**:302, 1942.

61. Levine, P.: The Rh Factor in Erythroblastosis and Transfusion Accidents, Proc. New York State A. Pub. Health Lab. **22**:42, 1942.

62. Wiener, A. S.: Blood Groups and Transfusions, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943.

63. Wiener, A. S., and Landsteiner, K.: Heredity of Variants of the Rh Type, Proc. Soc. Exper. Biol. & Med. **53**:167, 1943.

Hardly was the ink on this paper dry when the discovery of another serum, which agglutinated only 30 per cent of cells with which it was tested, led Wiener [64] to propose still another system of classification. He decided to "designate the new agglutinin as anti-$Rh_2$ and the agglutinogen detected by it as $Rh_2$. Thus, type $Rh_1$ is now subdivided into type $Rh_1$ $Rh_2$ (positive with anti-$Rh_2$ serum), and type $Rh_1$ proper (negative with anti-$Rh_2$ serum), while type $Rh_2$ is subdivided into type $Rh_2$ proper (positive with anti-$Rh_2$ serum) and Rh (negative with anti-$Rh_2$ serum). In the so-called Rh-negative type there are rare bloods agglutinated by the anti-$Rh_2$ serum. It is obvious that such individuals should now be deleted from the Rh-negative type, because the use of their blood for patients actively or passively sensitized to the $Rh_2$ agglutinogen might prove disastrous."

TABLE 1.—*Classification of the Types and Subtypes of Blood in Relation to the Rh Factor, According to Wiener and Landsteiner* [63]

| Designation of Agglutinin in the Serum | Positive Reactions, Approximate % | Reactions of Bloods from White Persons (New York City) | | | |
|---|---|---|---|---|---|
| | | About 70% | About 3% | About 14% | About 13% |
| 1. Anti-Rh..... | 84 | Positive | Negative | Positive | Negative |
| 2. Anti-$Rh_1$..... | 73 | Positive | Positive | Negative | Negative |
| 3. Anti-Rh'..... | 87 | Positive | Positive | Positive | Negative |
| Designation of types..... | | Rh positive | | | Rh negative |
| Designation of main subtypes | | $Rh_1$ | | $Rh_2$ | |
| | | Rh' | | | |

In subsequent papers [65] eight types of blood were described that were identified by their reaction to the three types of testing serums which Wiener recognized; anti-Rh serum agglutinated the blood of approximately 85 per cent, anti-$Rh_1$ agglutinated that of about 70 per cent, and anti-$Rh_2$ agglutinated that of about 35 per cent of white persons.

Early in 1944 Wiener, Sonn and Belkin [66] gave further evidence of the existence of these types in a statistical analysis of the reactions to the Rh factor exhibited by the blood of 275 children in 97 families.

Although the majority of anti-Rh serums seem to fall in one of three groups, it is probable that an attempt to include all minor varieties in a system of nomenclature will never be feasible. Gallagher and Jones [67] described three serums, one from guinea pigs giving positive reactions with the blood of 83 per cent of all persons tested, one human serum giving positive reactions with 84 per cent and a second human serum giving positive reactions with only 54 per cent of those tested. Fisk and Foord [68] studied four serums giving positive reactions with 83.0 per cent, 84.9 per cent, 86.0 per cent and 87.2 per cent of bloods respectively. A few cells reacted positively to one or another of these serums reacting negatively to guinea-pig serums, but for the most part animal and human serums gave similar results. They found, however, that of 312 cord bloods all of which gave positive reactions to guinea-pig serum, 8.8 per cent gave negative reactions with one human serum and 13.6 per cent with another human serum. The uniform agglutination of cord blood by animal serum has been subsequently corroborated by Wiener, Sonn and Belkin,[66] and it seems that animal serum is useless for typing the blood of infants at the time of birth. All specimens of cord blood showed much stronger agglutination in guinea pig serum than did adult cells.

It was originally believed that rabbit agglutinins produced against rhesus cells were identical with the anti-Rh agglutinins present in human blood. It has been definitely shown, however, that there are other differences besides the one just mentioned. Animal agglutinins act on about 85 per cent of adult human cells, and their activity parallels that of anti-Rh serum fairly closely, but Davidsohn and Toharsky [58] found that adsorption of human anti-Rh serum with human Rh-positive cells removed all of the agglutinins for monkey cells but only part of those for human cells.[69] Also, when human anti-Rh serum was adsorbed by monkey cells, the agglutinins for monkey cells were removed but not those for human blood. When animal serum produced by inoculation of guinea pigs with monkey blood was adsorbed by monkey cells, the agglutinins for for both monkey and human blood were completely removed, but when it was adsorbed with human cells the agglutinins for monkey cells were unaffected.

64. Wiener, A. S.: Distribution and Heredity of Variants of the Rh Type, Science **98**:182, 1943.

65. (*a*) Wiener, A. S.: Genetic Theory of the Rh Blood Types, Proc. Soc. Exper. Biol. & Med. **54**:316, 1943. (*b*) Wiener, A. S.; Sonn, E. B., and Belkin, R. B.: Heredity and Distribution of the Rh Blood Types, ibid. **54**:238, 1943.

66. Wiener, A. S.; Sonn, E. B., and Belkin, R. B.: Heredity of the Rh Blood Types, J. Exper. Med. **79**: 235, 1944.

67. Gallagher, F. W., and Jones, L. R.: Preparation and Use of Rh Testing Sera, J. Immunol. **46**:9, 1943.

68. Fisk, R. T., and Foord, A. G.: Observations on the Rh Agglutinogen of Human Blood, Am. J. Clin. Path. **12**:545, 1942.

69. The reaction was dependent on the kind of Rh-positive cells used, and it was similar to that demonstrated by Levine in the experiments in which he was able to adsorb one antibody from serum giving positive reactions with the blood of 87 per cent of persons tested and have another antibody left.

*General Distribution of the Rh Factor.*—Of 11,261 unselected white persons examined in the United States, Germany, England, Wales, Australia and Chile, 84.2 per cent had blood which was Rh-positive and 15.8 per cent had Rh-negative blood (table 2). Human serums reacted with a slightly higher percentage of blood cells than did animal serums, but in general the two gave similar results. Only standard anti-Rh serums were used.

Studies on Negroes,[70] American Indians [59] and Chinese [71] living in the United States revealed a higher incidence of Rh-positive blood in persons of these races (table 3) than in white persons in the same areas. The difference was especially notable in the full-blooded Indians and the Chinese. Only 1 person with Rh-negative blood was found among 120 Indians examined and only 1 among 150 Chinese. It may be possible that these two persons had some intermixture of white blood; that Indians and Chinese may uniformly have Rh-positive blood. American Indians of mixed parentage showed an incidence approximating that which would be expected on the basis of 60 per cent white blood, if one considers the incidence of Rh-positive blood in white persons as 85 per cent and in Indians as 100 per cent.

Vaccaro [72] found that only 7.5 per cent of 119 Chilean men and women had Rh-negative blood. Although this is a small group on which to base a conclusion, it may be possible that further studies will show a higher incidence of Rh-positive blood in Chileans than in any previously reported white population.

When the reaction to the anti-Rh serum agglutinating the blood of 70 to 73 per cent of white persons was investigated in Negroes, Indians and Chinese, an unexpected divergence was revealed (table 4). The blood of Negroes and Indians yielded a much lower percentage of positive reactions, while that of the Chinese reacted almost as uniformly to this serum as to the other. This suggests a definite qualitative difference in the antigenic components of the cells which react to these two serums.

The present proportion of persons with Rh-positive and with Rh-negative blood in the white race and in other races is a matter of interest. Differences in the distribution of the blood groups

TABLE 2.—*Incidence of the Rh Factor in the Blood in White Populations*

| Author | Country | Total Number of Subjects | Blood Type: Rh+ No. | Rh+ % | Rh− No. | Rh− % | Source of Testing Serum |
|---|---|---|---|---|---|---|---|
| Levine [60] | United States | 1,035 | 897 | 86.6 | 138 | 13.4 | Human |
| Wiener [60] | United States | 777 | 665 | 85.6 | 112 | 14.4 | Animal and human |
| Fisk and Foord [68] | United States | 927 | 788* | 85.0 | 139* | 15.0 | Animal |
| Gallagher and Jones [67] | United States | 156 | 130* | 83.0 | 26* | 17.0 | Animal |
| Gallagher and Jones [67] | United States | 118 | 100* | 85.0 | 18* | 15.0 | Human |
| Boorman [47a] | England | 1,610 | 1,371 | 85.15 | 239 | 14.85 | Human |
| Hoare [136a] | Wales | 1,122 | 949 | 84.6 | 173 | 15.4 | Animal |
| Simmons, Graydon, Jakobowicz and Bryce [133] | Australia | 3,641 | 2,998 | 82.34 | 643 | 17.66 | Human |
| Dahr [136b] | Germany | 1,756 | 1,475* | 84.0 | 281* | 16.0 | Animal |
| Vaccaro [72] | Chile | 119 | 110* | 92.5 | 9* | 7.5 | |
| Total | | 11,261 | 9,483 | 84.2 | 1,778 | 15.8 | |

* Figures calculated from authors' data.

TABLE 3.—*Racial Differences in Reaction to Standard Anti-Rh Serum of the Type Agglutinating the Cells of Eighty-Five per cent of White Persons*

| Author | Race | Total Number of Subjects | Reaction to Anti-Rh Serum: Positive No. | Positive % | Negative No. | Negative % |
|---|---|---|---|---|---|---|
| Combined data | White | 7,620 | 6,485 | 85.1 | 1,135 | 14.9 |
| Landsteiner and Wiener [57] | Negro | 113 | 104 | 92.0* | 9 | 8.0* |
| Levine [70b] | Negro | 264 | 252* | 95.5 | 12* | 4.5 |
| Landsteiner, Wiener and Matson [59] | American Indian | | | | | |
| | Full blooded | 120 | 119 | 99.2 | 1 | 0.8 |
| | Mixed blooded | 155 | 148 | 95.5* | 7 | 4.5* |
| Levine and Wong [71] | Chinese | 150 | 149 | 99.3 | 1 | 0.7 |

* Figures calculated from authors' percentages.

TABLE 4.—*Racial Differences in Reaction to Anti-Rh$_1$ Serum* *

| Author | Race | Total Number of Subjects | Reaction of Blood: Positive, % | Negative, % |
|---|---|---|---|---|
| Wiener [28] | White | 68 | 70 | 30 |
| Levine et al.[31b] | White | 334 | 73 | 27 |
| Levine [70b] | Negro | 118 | 46 | 54 |
| Landsteiner, Wiener and Matson [59] | American Indian | 69 | 58 | 42 |
| Levine and Wong [71] | Chinese | 150 | 93 | 7 |

* All serums used in these determinations were of the type agglutinating the cells of approximately 70 per cent of white persons.

70. (*a*) Landsteiner and Wiener.[57] (*b*) Levine, P.: On Human Anti-Rh Sera and Their Importance in Racial Studies, Science **96**:452, 1942.

71. Levine, P., and Wong, H.: The Incidence of the Rh Factor and Erythroblastosis Fetalis in Chinese, Am. J. Obst. & Gynec. **45**:832, 1943.

72. Vaccaro, H.: Hemoaglutinogeno Rh y eritroblastosis foetalis, Rev. chilena de pediat. **14**:717, 1943.

in different races have been attributed to the effects of geographic location, such as isolation of small groups of people with consequent inbreeding and increasing predominance of certain groups and migration of specialized races resulting in intermixture of characteristics and to mutation from the 0 form after the establishment of races. Wiener [73] called attention to the fact that in order to produce the incidence of Rh-negative blood which exists in the white race, the rate of mutation from Rh-positive to Rh-negative would have to be much higher than that of any other mutation previously described. He concluded that the incidence could be explained best on the basis of intermixture of races which originally consisted largely of persons with Rh-positive or of persons with Rh-negative blood. Haldane [74] also mentioned this as a reasonable possibility. Hogben [75] recently stated that he believed the rate of mutation would not have to be inordinately high if it was interpreted as a mutation at the Rh locus from any one of a series of five or more dominant alleles. Fisher, Race and Taylor [76] have taken exception to this view and have stated that it is unjustified.

*Inheritance of the Rh Factor.*—The Rh factor appears to be inherited in a mendelian manner. Before subgroups of Rh had been recognized, or before it was possible to differentiate them, Landsteiner and Wiener [57] and Wiener and Sonn [77] determined the number of persons with Rh-positive and with Rh-negative blood in 100 families with 475 children and found a close correlation between the number observed in each group and the number to be expected on the basis of mendelian inheritance. They concluded that inheritance was by means of two allelic genes, Rh and rh, Rh representing the positive character and being dominant over rh, the negative character. Thus the two genotypes RhRh and Rhrh would be included in the phenotype Rh +, while only the genotype rhrh could occur with the phenotype Rh —. Two persons of the phenotype Rh + may have offspring with Rh-negative blood, but 2 persons of the phenotype Rh — cannot have children with Rh-positive blood. In a population of which 84.8 per cent of the persons are of the phenotype Rh +; 36.9 per cent will be RhRh, 47.7 per cent Rhrh and 15.4 per cent rhrh in genotype. If mating is random, 13.1 per cent of all marriages will be between women of the phenotype Rh — and men of the phenotype Rh + and in 9.36 per cent of all pregnancies a woman of the genotype rhrh will carry a child of the genotype Rhrh.[74]

After the discovery that some serums were capable of agglutinating the blood of only 70 per cent instead of 85 per cent of all persons, Wiener and Landsteiner [63] and Wiener [64] stated that the ability of cells to be agglutinated by one or the other of these serums also appeared to follow a definite mendelian pattern of inheritance. According to the terminology used at that time inheritance was by means of three allelic genes, $Rh_1$, $Rh_2$ and rh. $Rh_1$ (the gene for the antigen agglutinable by the serum reacting with 70 per cent of all cells but not by that reacting with 85 per cent of all cells), and both $Rh_1$ and $Rh_2$ were believed to be dominant over rh. The antiserum which gave a positive reaction with the blood of 87 per cent of the persons tested was believed to isolate a third type of antigen (called $Rh_{12}$ by Levine); subsequently, therefore, four allelic genes, three Rh genes and one rh, were postulated.[62] The serum found later to agglutinate the cells of only 30 per cent of the persons tested was stated to identify still another variety of Rh antigen, which also followed a definite pattern of inheritance. By the use of this serum in addition to the others previously described, Wiener [65a] and Wiener, Sonn and Belkin [65b] decided that there were six allelic genes, all of equal dominance, and designated them $Rh_1$, $Rh_2$, Rh, Rh′, Rh″ and rh (table 5). A study by the latter authors [66] of 97 families with 275 children showed no discrepancies in inheritance according to the theory of 6 alleles.

A group of English investigators, Race, Taylor, Boorman and Dodd,[78] have observed, in independent investigations, much the same results obtained by Wiener and his associates. They have found two serums each of which agglutinates the cells of 30 per cent of the persons tested. These have been designated K and J and appear to correspond to the anti-$Rh_2$ serum of Wiener.

Another serum, St, dissimilar to any as yet reported by Wiener, was observed by Race and Taylor.[79] It agglutinates all Rh-negative blood and Rh-positive blood from persons who are heterozygous and from about 20 per cent of those who appear to be homozygous. They and their col-

73. Wiener, A. S.: The Rh Factor and Racial Origins, Science **96**:407, 1942.

74. Haldane, J. B.: Selection Against Heterozygosis in Man, Ann. Eugenics **11**:333, 1943.

75. Hogben, L.: Mutation and the Rhesus Reaction, Nature, London **152**:721, 1943.

76. Fisher, R. A.; Race, R. R., and Taylor, G. L.: Mutation and the Rhesus Reaction, Nature, London **153**:106, 1944.

77. Wiener, A. S., and Sonn, E. B.: Heredity of the Rh Factor, J. Genetics **45**:157, 1943.

78. Race, R. R.; Taylor, G. L.; Boorman, K. E., and Dodd, B. E.: Recognition of Rh Genotypes in Man, Nature, London **152**:563, 1943.

79. Race, R. R., and Taylor, G. L.: A Serum That Discloses the Genotype of Some Rh Positive People, Nature, London **152**:300, 1943.

laborators [80] have postulated that persons whose blood fails to react with this serum are of the genotype $Rh_1Rh_1$, and they have stated that with the use of this serum in addition to the others previously recognized, the Rh genotype of at least 80 per cent of the population can be determined. They have observed the 6 allelomorphs described by Wiener and believe there is a seventh one ($Rh_7$) which can be discovered only by the use of St serum. Loutit,[81] reviewing the papers by Wiener and Race and their associates, concluded that the investigations were in such close agreement that the varieties of genes described could be accepted as established.

## RELATIONSHIP OF THE RH FACTOR TO ERYTHROBLASTOSIS

*Diagnosis of Erythroblastosis.*—Erythroblastosis fetalis is a disease characterized by the abnormal destruction and regeneration of erythrocytes. Until recently there was some disagreement as to which was the primary process,[82] but it appears fairly certain in view of recent studies that hemolysis initiates all the other pathologic changes. Several authors [83] have suggested replacing the name "erythroblastosis" with "acute hemolytic anemia of the fetus and newborn" in order to indicate that hemolysis is the basic phenomenon.

The pathologic manifestations of erythroblastosis are direct results of excessive destruction of erythrocytes and of an attempt on the part of the body to compensate for this loss. Anemia, increased bilirubin in the blood and in various fixed tissues of the body, abnormal erythropoiesis in many organs, including the spleen and liver, and an increase in immature forms of erythrocytes in the circulating blood are among the signs most commonly observed. The extreme edema which is present in many of the infants with more severe erythroblastosis has not been completely explained; factors as to its origin which have been suggested include renal failure, injury of the general capillary bed and a decrease in plasma proteins occurring in conjunction with cellular hemolysis. The interrelationship of the various pathologic changes has been discussed recently by Davidsohn.[84]

The general symptomatology has been well discussed on several occasions,[85] and in a typical case the diagnosis of erythroblastosis is easily

TABLE 5.—*The Rh Blood Types and Their Theoretic Genotypes (Wiener, Sonn and Belkin [65b])*

| Phenotype | Reactions with Rh Antiserums | | | | | Approximate Frequency in White Persons (New York City), % | Theoretically Possible Genotypes |
|---|---|---|---|---|---|---|---|
| | Anti-Rh | Anti-$Rh_1$ | Anti-$Rh_2$ | Anti-Rh′ | Anti-Rh″ | | |
| rh | − | − | − | − | − | 12.75 | rhrh |
| $Rh_1$ | + | + | − | + | ± | 50 | $Rh_1Rh_1$, $Rh_1rh$, $Rh_1Rh$, $Rh_1Rh'$, $Rh'Rh$ |
| $Rh_2$ | + | − | + | + | + | 15.5 | $Rh_2Rh_2$, $Rh_2rh$, $Rh_2Rh$, $Rh_2Rh''$, $Rh''Rh$ |
| $Rh_1Rh_2$ | + | + | + | + | + | 17 | $Rh_1Rh_2$, $Rh_1Rh''$, $Rh'Rh_2$ |
| Rh | + | − | − | + | + | 2.5 | RhRh, Rhrh |
| Rh′ | − | + | − | + | − | 2 | Rh′Rh′, Rh′rh |
| Rh″ | − | − | + | − | + | 0.25 | Rh″Rh″, Rh″rh |
| Rh′Rh″ * | − | + | + | + | + | ..... | Rh′Rh″ |

* This theoretically possible type has not yet been encountered, which is not surprising considering the extremely low value of the calculated frequency of the genotype Rh′Rh″.

80. Race, R. R.; Taylor, G. L.; Cappell, D. F., and McFarlane, M. N.: Recognition of a Further Common Rh Genotype in Man, Nature, London **153**:52, 1944.

81. Loutit, J. F.: Human Blood Groups, Nature, London **153**:97, 1944.

82. (*a*) Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, J. Pediat. **1**:269, 1932. (*b*) Hawksley, J. C., and Lightwood, R.: A Contribution to the Study of Erythroblastosis: Icterus Gravis Neonatorum, Quart. J. Med. **3**:155, 1934.

83. (*a*) Boorman and Dodd.[37] (*b*) Race, Taylor, Cappell and McFarlane.[81] (*c*) Kariher, D. H., and Spindler, H. A.: Erythroblastosis Fetalis and the Blood Factor Rh, Am. J. M. Sc. **205**:369, 1943.

84. Davidsohn, I.: The Rh Factor, M. Clin. North America **28**:232, 1944.

85. (*a*) Diamond, Blackfan and Baty.[82a] (*b*) Hawksley and Lightwood.[82b] (*c*) Clifford, S. H., and Hertig, A. T.: Erythroblastosis of the Newborn, New England J. Med. **207**:105, 1932. (*d*) Ross, S. G., and Waugh, T. R.: Certain Types of Icterus Gravis, Am. J. Dis. Child. **51**:1059 (May) 1936. (*e*) Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death, Chicago, University of Chicago Press, 1940.

established. The milder forms may be difficult or impossible to diagnose on clinical grounds, and occasionally it may be impossible to establish the diagnosis even at autopsy.[86] No single feature, including severe unexplained anemia, severe icterus or fetal hydrops,[87] can be considered pathognomonic, and although the possibility of the disease should be considered whenever any one of these symptoms is present in the fetus or the newborn infant, a definite diagnosis must be made with caution.

Anemia is more constantly present than any other symptom, but icterus almost always develops rapidly if the infant is born alive. The icteric index frequently becomes extremely high, indicating that excessive hemolysis and inability of the liver to eliminate the products of cellular destruction both exist. If the blood of the infant is examined immediately after birth, erythroblasts and normoblasts are usually found, but if smears are not made for several days the immature cells may have disappeared. However, an increase in immature red cells in the peripheral blood when unassociated with other symptoms cannot be considered indicative of erythroblastosis. Casey and Crowson [88] examined the blood of 116 infants within twenty-four hours after birth and found an appreciable increase in the number of immature cells in 4 infants, all of whom subsequently died. The causes of death were not given, but it can be concluded that the infants did not have erythroblastosis.

Enlargement of the spleen is one of the most significant diagnostic criteria. If the spleen extends 2 cm. or more below the costal margin or weighs 25 Gm. or more, either erythroblastosis or syphilis is almost certain to be the causative factor. In several thousand autopsies on fetuses and newborn infants I have never seen this degree of enlargement from any other cause. If it were necessary to make a diagnosis of erythroblastosis on observation of a single organ or on a single laboratory finding, a study of the spleen would yield the highest percentage of correct results.

Before a definite diagnosis is made, however, the general symptom complex must be present. Although subsequent events (especially the birth of a sibling with definite erythroblastosis) may show that the disease existed even though the symptoms were incomplete or atypical, it is unjustifiable to diagnosis this condition on inadequate grounds. The grave outlook for future child-bearing which exists once the presence of erythroblastosis is established is sufficient reason for making the diagnosis with caution.

Study of the Rh factor in the parents and in the affected child may give contributory evidence of the presence or absence of the disease. Finding that the mother's blood is Rh negative and that the father and the child have Rh-positive blood lends support to the diagnosis, and this is augmented by the demonstration of anti-Rh agglutinins in the maternal blood. Discovering that the mother's blood is Rh positive is strong but not final evidence against erythroblastosis in the infant. Mollison [89] stated the belief that if no antigen which is lacking in the mother is present in the fetus the diagnosis of erythroblastosis can be practically excluded. The Rh status of the family, however, is never in itself a sufficient basis for making a diagnosis.

It has always been the belief of the author that erythroblastosis should be considered a specific pathologic entity, and this belief has been strengthened by the recent work on the Rh factor. The oft recurring statement that erythroblastosis is due to many conditions and is only a symptom complex associated with various etiologic agents indicates unfamiliarity with the details of the disease complex. Practically any abnormal state characteristic of erythroblastosis can be duplicated by some other condition, but it is unwarranted to say that erythroblastosis is not a disease entity only because erythroblastemia may be found in association with infections, abnormal erythropoiesis in association with syphilis and jaundice in association with internal hemorrhage. Whether the cause is ultimately proved to be an antigen-antibody reaction, as currently believed, or whether some other etiologic agent is eventually discovered, there is a definite condition for which a uniform cause may be expected.

*Incidence of Erythroblastosis.*—The true incidence of erythroblastosis is somewhat difficult to determine. It can be accurately calculated only in relation to a given number of births, and then only when all macerated as well as nonmacerated fetuses and infants who have died have been examined at autopsy by a pathologist fully aware of the diagnostic criteria of erythroblastosis and when all surviving infants have been under ade-

86. Potter, E. L.: Reducing the Hazards of the First Two Days of Life: The Role of the Rh Factor, J. Pediat. **23**:486, 1943.

87. Potter, E. L.: Universal Edema of the Fetus Unassociated with Erythroblastosis, Am. J. Obst. & Gynec. **46**:130, 1943.

88. Casey, A. E., and Crowson, S. H.: Nucleated Erythrocytes in Newly Born Infants in Relation to Maternal Rh Compatibility, Proc. Soc. Exper. Biol. & Med. **54**:320, 1943.

89. Mollison, P. L.: The Etiology of Erythroblastosis Fetalis and Certain Haemolytic Transfusion Reactions with Special Reference to the Rh Factor, Proc. Roy. Soc. Med. **36**:221, 1943.

quate clinical observation. Javert [90] reported an incidence of 1 per 438 deliveries at the New York Hospital during a five year period ending in 1940; this was a 400 per cent increase over the incidence observed from 1933 to 1936. Potter and Adair [91] reported 1 death from erythroblastosis for each 1,000 deliveries from 1931 to 1941, but they have had an incidence of 1 for each 500 for the years 1941, 1942 and 1943. From 1941 to 1943 inclusive there have been 10,378 births at the Chicago Lying-in Hospital, with loss of 360 fetuses and infants (all fetuses and infants weighing over 400 Gm. are included). A diagnosis of erythroblastosis was made for 22 infants who died or were stillborn. This figure represents 6.1 per cent of the total deaths but only 0.21 per cent of the total births.[92] The diagnosis was made for 6 additional infants who did not die. This raises the total incidence to 1 per 370 births. During this period postmortem examinations in no way differed from those performed from 1934 to 1941, but infants in the nurseries were more closely scrutinized for the possible presence of erythroblastosis. Studies of the blood were made for all infants who were pale or had early jaundice or who for any reason were doing poorly.

Only 2 of the 28 infants were delivered by women who had not been previously pregnant, which makes the incidence 1 per 2,380 first-born infants and 1 per 245 subsequently born infants. Schwartz and Levine [93] reported that in a series of 2,000 deliveries with a considerably greater total fetal and infant mortality 4.4 per cent of the infants who died (0.35 per cent of the infants born) had erythroblastosis. Six additional deaths were considered probably due to erythroblastosis, almost entirely, as far as can be determined, on the basis that the mother had Rh-negative blood. The addition of this case made 8.2 per cent of the deaths due probably to erythroblastosis and increased the incidence of fatal erythroblastosis to 0.65 per cent of the total number of births. This incidence is three times that observed at the Chicago Lying-in Hospital. The authors state that the figures "support Levine's [94] contention that the incidence of erythroblastosis will be considerably higher if based on the results of the Rh tests." Many women with Rh-positive blood lose babies from unexplained causes both before and after birth, and it is unreasonable to assume that because a woman has Rh-negative blood the cause of the death of her infant must be related to this fact.

*Etiology of Erythroblastosis.*—The previously suggested causes of erythroblastosis include maternal toxemia, nephritis, heart disease and anemia, fetal nephritis or renal failure, hepatic dysfunction, malformation of the heart, malformation or neoplasm of hemopoietic tissues, sepsis, syphilis, toxemia or allergy, defect of the primitive germ plasm or abnormality of the zygote, hereditary transmission by a dominant gene or by a recessive gene, abnormal persistence of embryonal hemopoiesis, exhaustion of a passively transmitted maternal hormone necessary for hemopoiesis or the absence of a hormone inhibiting hemolysis, breakdown in the placental barrier resulting in abnormal intermixture of maternal and fetal blood and fetal response to maternal immunization against fetal hemoglobin or against the A or B substance in fetal blood cells.

The present concept of the causation of erythroblastosis is the only one of all those thus far considered which seems adequate. This theory presumes that an antigenic substance, Rh, is absent from the blood of a given woman and present in that of her husband; when conception takes place an Rh-positive sperm fertilizes an Rh-negative ovum and the resulting fetus is of the phenotype Rh +. Fetal blood bearing the Rh antigen escapes from the placenta into the maternal circulation. Immunization of the mother takes place, since the Rh factor is an antigen foreign to her cells. Immune bodies thus produced return to the fetus, react with its Rh-positive cells and destroy them. When the antigen-antibody reaction in the fetus is sufficient to destroy erythrocytes at a proportionately faster rate than the hemopoietic tissue can produce them, the symptoms of erythroblastosis result.

### EVIDENCE SUPPORTING THE CONTENTION THAT ERYTHROBLASTOSIS IS AN RH ANTIGEN-ANTIBODY REACTION IN THE FETUS

1. The clinical and pathologic manifestations can all be explained as direct results of hemolysis or as compensatory mechanisms designed to combat the effects of hemolysis. Anemia, icterus and probably edema are direct results of hemolysis; excessive erythropoiesis with associated erythroblastemia, hepatomegaly and splenomegaly are the result of an attempt to replace the hemolyzed cells.

2. The great majority of women giving birth to infants with erythroblastosis have Rh-negative

90. Javert, C. T.: Erythroblastosis Neonatorum: An Obstetrical-Pathological Study of Forty-Seven Cases, Surg., Gynec. & Obst. **74**:1, 1942.

91. Potter, E. L., and Adair, F. L.: Clinical-Pathological Study of the Infant and Fetal Mortality for a Ten Year Period at the Chicago Lying-In Hospital, Am. J. Obst. & Gynec. **45**:1054, 1943.

92. Potter, E. L.: Unpublished data.

93. Schwartz, H. A., and Levine, P.: Studies on the Rh Factor, Am. J. Obst. & Gynec. **46**:827, 1943.

94. Levine, P.: Pathogenesis of Erythroblastosis, New York State J. Med. **42**:1928, 1942.

blood. Only 15 per cent of all white women in this country have Rh-negative blood, while of mothers giving birth to infants with erythroblastosis over 90 per cent have Rh-negative blood. This difference is far too great to be due to chance, and a necessary relationship between erythroblastosis and the Rh-negative state of the mother's blood is evident. Of 711 women reported to have given birth to infants with erythroblastosis whose Rh status has been determined, 651 had Rh-negative blood (table 6).

TABLE 6.—*Rh Status of Infants with Erythroblastosis and of the Parents*

| | Mother's Blood | | | Father's Blood | | Infant's Blood | |
|---|---|---|---|---|---|---|---|
| | Rh+ | Rh− | Anti-Rh Agglutinins | Rh+ | Rh− | Rh+ | Rh− |
| Levine [94] | 35 | 315 | .. | 204 | 0 | 139 | .. |
| Potter et al.[96a] | 5 | 55 | 10 | 21 | 1 | 25 | 2 |
| Race et al.[51] | 6 | 44 | 38 | .. | .. | .. | .. |
| Boorman et al.[96] | 3 | 97 | 93 | .. | .. | .. | .. |
| Wiener [62] | 6 | 37 | .. | .. | .. | .. | .. |
| Gimson [95b] | 0 | 19 | 18 | .. | .. | 19 | .. |
| Vaccaro [72] | .. | 14 | 14 | 14 | .. | 14 | .. |
| Javert [109] | 3 | 9 | .. | .. | .. | .. | .. |
| Fisk and Foord [68] | .. | 9 | 6 | .. | .. | .. | .. |
| Diamond [46] | .. | 6 | 5 | .. | .. | .. | .. |
| Brown and Levine [119f] | 1 | 5 | .. | 6 | .. | .. | .. |
| Kariher and Spindler [83c] | .. | 6 | 6 | 6 | .. | .. | .. |
| Mollison [89] | .. | 6 | 6 | .. | .. | .. | .. |
| Schwartz and Levine [98] | .. | 6 | 3 | .. | .. | .. | .. |
| Brewer [140b] | .. | 5 | .. | .. | .. | .. | .. |
| Hoare [126a] | .. | 5 | 5 | .. | .. | .. | .. |
| Witebsky and Heide [55b] | .. | 2 | 2 | 2 | .. | 2 | .. |
| Witebsky et al.[55a] | .. | 1 | 1 | .. | .. | .. | .. |
| Damashek et al.[140c] | 1 | 1 | .. | .. | .. | 1 | .. |
| Crawford and Stewart [140o] | .. | 2 | .. | .. | .. | 2 | .. |
| Aagaard [129a] | .. | 2 | 2 | .. | .. | .. | .. |
| Koucky [39] | .. | 2 | 2 | 1 | .. | .. | .. |
| Kariher [44] | .. | 1 | 1 | .. | .. | .. | .. |
| Newerla [140l] | .. | 1 | 1 | .. | .. | .. | .. |
| Hertzog [98b] | .. | 1 | .. | .. | .. | .. | 1 |
| Total | 60 | 651 | 213 | 254 | 1 | 202 | 3 |

3. Anti-Rh agglutinins can be demonstrated in the circulation of some women giving birth to infants with erythroblastosis. Most of the English investigators [95] have reported a much higher incidence of agglutinins than has been found by any one in the United States. Boorman, Dodd and Mollison [47a] found that 44 of 46 patients with Rh-negative blood had agglutinins seven to twenty-one days after delivery. A subsequent report [96] of 100 women proved to have had infants with erythroblastosis indicates that 97 had Rh-negative blood and that the blood of only 4 of the 97 failed to contain demonstrable anti-Rh agglutinins. In the series studied by Potter, Davidsohn and Crunden [96a] the low incidence of 10 patients with blood containing agglutinins in 60 with Rh-negative blood may well be due to the fact that the majority of the tests were made several months or years after the birth of the last child. Levine, Burnham, Katzin and Vogel [81b] reported the postpartum presence of agglutinins in 41 of 141 women and showed a decreasing incidence with progressive prolongation of the interval between delivery and testing. Of 70 women tested within two months after delivery, 33 had anti-Rh agglutinins in the blood, while agglutinins could be demonstrated in the blood of only 2 of 41 when the interval was in excess of one year. The low incidence of agglutinins may be caused by insufficiently sensitive methods of testing, or it may mean that the antibodies are attached to tissues and become free in the circulation only under special stimulation.

4. Anti-Rh agglutinins are present in the milk of some women who give birth to infants with erythroblastosis. Three cases have been reported by Witebsky, Anderson and Heide [55] and 2 have been observed by Potter and Davidsohn [56] in which agglutinins were present in milk. Their presence in the milk has doubtless been demonstrated in additional cases which are unreported, and if proper investigations were made they might well be shown to be present in the milk of a large percentage of women who have a high serum titer of anti-Rh agglutinins.

5. Anti-Rh agglutinins have been found in the circulation of infants with erythroblastosis soon after birth. Twins, both of whom had demonstrable anti-Rh agglutinins in their blood, were observed by Boorman, Dodd and Mollison,[47a] and Diamond [47b] states that he has observed the presence of anti-Rh agglutinins on several occasions soon after birth. This is somewhat surprising, for one would expect an antigen-antibody reaction to remove free antibodies from the circulation.

6. Rh-negative blood survives a normal length of time when administered to infants with erythroblastosis. It has been shown [97] that fresh blood cells introduced into the circulation by transfusion can be identified eighty to one hundred

95. (*a*) Race, Taylor, Cappell and McFarlane.[51] (*b*) Gimson, J. B.: Haemolytic Disease of the Newborn (Erythroblastosis Foetalis): Its Treatment with Rhesus-Negative Blood, Brit. M. J. **2**:293, 1943.

96. Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: The Incidence of Haemolytic Disease of the Foetus ("Erythroblastosis Foetalis") in Different Families: The Value of Serological Tests in Diagnosis and Prognosis, J. Obst. & Gynaec. Brit. Emp. **51**:1, 1944.

96a. Potter, E. L.; Davidsohn, I., and Crunden, A. B.: The Importance of the Rh Blood Factor in Erythroblastosis, Am. J. Obst. & Gynec. **45**:254, 1943.

97. (*a*) Wiener, A. S.: Longevity of the Erythrocyte, J. A. M. A. **102**:1779 (May 26) 1934. (*b*) Mollison, P. L.: Some Revised Principles of Blood Transfusion, Proc. Roy. Soc. Med. **36**:335, 1943. (*c*) Mollison, P. L., and Young, I. M.: In Vivo Survival in the Human Subject of Transfused Erythrocytes After Storage in Various Preservative Solutions, Quart. J. Exper. Physiol. **31**:359, 1942.

and twenty days later unless they have been abnormally hemolyzed. When Rh-negative blood is given infants with erythroblastosis the cells are more apt to survive for normal periods than when Rh-positive cells are used. Mollison [89] reported that when mixtures of Rh-positive and Rh-negative cells were given the Rh-positive cells, except in 1 instance, disappeared almost immediately while the Rh-negative cells were present three months later. If there were no anti-Rh agglutinins present or if there were no relationship of the Rh factor to erythroblastosis, Rh-positive blood should survive as well as Rh-negative.

7. The husbands of practically all women with Rh-negative blood with affected infants and practically all of the affected infants have Rh-positive blood. If there were no relation between the possession of Rh-positive blood by the father and erythroblastosis in the offspring, the husbands of at least 15 per cent of women with Rh-negative blood who have infants with erythroblastosis and almost 60 per cent of the children should have Rh-negative blood. (The incidence of Rh-negative blood in husbands should be the same as that in the general population. All of the children born of these fathers should have Rh-negative blood, and since almost half of the men whose phenotype is Rh + are heterozygous for the Rh factor about half of those born of fathers with Rh-positive blood should also have Rh-negative blood.) Levine [94] found that all husbands of 204 women with Rh-negative blood who gave birth to babies with erythroblastosis had Rh-positive blood. Occasional husbands and infants with Rh-negative blood have been reported,[98] but a great preponderance have Rh-positive blood.

8. The disease is rare in first-born children. The almost uniform sparing of first-born children can be explained only on the basis that something transpires during a pregnancy to make conditions appropriate for the development of the disease in children born subsequently. The process of immunization is known to require time, and it is probable that during the course of a single pregnancy an erythroblastosis-producing concentration of antibodies does not ordinarily develop.[99] An extremely mild form of the disease occurs occasionally in a first child, and a severe form may exist if the mother has been previously immunized by the introduction of Rh-positive blood by transfusion. However, unless the mother has previously received a transfusion, death from erythroblastosis is extremely rare in the first offspring. It seems clear that the condition responsible for maternal immunization ordinarily occurs prior to the pregnancy in which erythroblastosis is first manifested.

9. Once the disease occurs it is repeated in all subsequently born siblings with Rh-positive blood. The degree and duration of an acquired immunity vary with the potency of the antigen and with the capability of the body to produce antibodies. It seems almost certain that the immunity acquired for the Rh antigen either is permanent or is renewed by some condition inherent in all pregnancies. It is inconceivable that any condition produced by the individual action of a genetic factor, infection or any other known etiologic agent should fail to act in a first pregnancy and be invariably repeated in all subsequent pregnancies. It is likewise untenable that if the action of antibodies lasted for only a short time new antibodies would invariably be formed by the recurrence of the same type of stimulus which was the inciting agent in the first instance. It must be concluded, therefore, (1) that immunity is permanent, (2) that pregnancy produces an anamnestic reaction resulting in further production of antibodies or (3) that enough fetal cells escape into the maternal circulation in all pregnancies to stimulate the production of antibodies in a mother previously immunized but insufficient in most instances to initiate the process.

10. Fetuses with Rh-negative blood escape the disease. There are 5 reports in the literature describing pairs of fraternal twins in which an infant with Rh-positive blood suffered from erythroblastosis but the one with Rh-negative blood was normal.[100] It is known that occasionally a child escapes whose siblings have had the disease, and although there are few reports to confirm this it is probable that these infants have Rh-negative blood. Potter [92] recently observed the first normal child in a fairly large series of infants born to mothers who had borne an infant with erythroblastosis. The mother of this child had had 3 normal children by one husband and 1 normal child by a second husband. The fifth pregnancy ended in the delivery of a hydropic fetus with typical erythroblastosis. The mother's blood was Rh negative and had a high titer of anti-Rh agglutinins six weeks after the fifth

98. (*a*) Potter, Davidsohn and Crunden.[96a] (*b*) Hertzog, A. J.: Problems Encountered in Explaining Certain Cases of Erythroblastosis Fetalis on the Rh Theory, Minnesota Med. **26**:1057, 1943.

99. Levine, P.: Iso-Immunization in Pregnancy and the Pathogenesis of Erythroblastosis Fetalis, in Karsner, H. T., and Hooker, S. B.: The 1941 Year Book of Pathology and Immunology, Chicago, Year Book Publishers, Inc., 1941, p. 505.

100. (*a*) Kariher.[44] (*b*) Levine.[50] (*c*) Potter, E. L.: A Double Ova Pregnancy in Which the Rh + Twin Developed Erythroblastosis, J. Pediat. **24**:449, 1944.

delivery. The sixth child has been entirely well since birth and is still normal at 10 months of age. The blood of the mother six months after the sixth delivery had a high titer of anti-Rh agglutinins. The infant's blood is Rh negative. The husband's blood is Rh positive, but it is also positive to Diamond's St serum (see subsequent discussion) indicating that he is heterozygous (Rhrh). These cases give further proof that the fetus of a mother who has once become immunized must have Rh-positive blood to acquire erythroblastosis and that a fetus with Rh-negative blood will escape the disease even though exposed to an environment favorable for its development.

Further proof would exist if after having had one or more infants with erythroblastosis a woman could deliver a normal child following impregnation with Rh — sperm.

11. The administration of Rh-positive blood to a woman whose blood is Rh negative may produce sufficient immunization to cause erythroblastosis in a subsequent fetus. In the majority of instances in which a woman has had an infant with erythroblastosis in a first pregnancy a history of one or more previous transfusions can be obtained. A few women with Rh-negative blood who have given birth to several normal children and have subsequently been given a transfusion with Rh-positive blood without ill effect have in the next pregnancy delivered an infant with erythroblastosis.[101] If these patients had been immunized against the Rh factor by the previous pregnancies, a reaction to the first transfusion of Rh-positive blood should have occurred.

12. The transfusion of Rh-positive blood into a woman whose blood is Rh-negative and who is the mother of a baby with erythroblastosis may cause a hemolytic reaction, even though the blood given appears compatible by all known tests. Anti-Rh agglutinins cannot be demonstrated in the blood of many women who have given birth to infants with erythroblastosis. The "biologic test" recommended by Wiener, Silverman and Aronson[102] may give evidence of the presence of active antibodies, even though they are not demonstrable in vitro. In a typical instance[92] a patient who had previously had 3 normal children gave birth at term to a slightly macerated fetus with erythroblastosis. The mother's blood was O Rh negative and contained no demonstrable anti-Rh agglutinins. The husband's blood was A Rh positive. Eight days after delivery the patient was given 50 cc. of O Rh-positive blood which was compatible on cross matching by the incubation-centrifugation method. She had no reaction, and the icteric index had only risen from 6.3 to 8.1 an hour after the transfusion. At this time 50 cc. more of the same blood was injected. A severe chill followed immediately; the temperature rose to 40.2 C. (104 F.), and at the end of the second hour the icteric index was 13.2. The temperature had returned to normal three hours later. The patient had been previously alkalinized, and there was no reduction in urinary output. Blood drawn two days after the biologic test still failed to show anti-Rh agglutinins. This case, as well as others which have been reported, gives evidence that immunization to the Rh factor may exist although laboratory methods used at present cannot demonstrate the existence of agglutinins.

101. (*a*) Diamond.[46] (*b*) Potter, E.: Unpublished data.

102. Wiener, A. S.; Silverman, I. J., and Aronson, W.: Hemolytic Transfusion Reactions: II. Prevention with Special Reference to a New Biological Test, Am. J. Clin. Path. **12**:241, 1942.

### EVIDENCE FAILING TO SUPPORT THE CONTENTION THAT ERYTHROBLASTOSIS IS AN RH ANTIGEN-ANTIBODY REACTION

1. Only a small percentage of women with Rh-negative blood give birth to infants with erythroblastosis. In approximately 9 per cent of all births an infant with Rh-positive blood is delivered by a mother with Rh-negative blood. Since the incidence of erythroblastotic infants seems to be approximately 1 to 400 births, the disease develops in only about 1 of 40 infants for whom the possibility of its occurrence exists. This low incidence is due to several factors: A. Erythroblastosis almost never occurs in a first pregnancy; thus women bearing only 1 child will have no infant with this disease. B. The total parity of the majority of women is low. The more pregnancies to which a woman with Rh-negative blood is subjected, the greater the likelihood that she will have a child with erythroblastosis. C. Since not all women with Rh-negative blood have infants with erythroblastosis in even a second or a subsequent pregnancy, it is necessary to postulate (*a*) that some Rh-positive fetal cells are not antigenic, (*b*) that in some instances the maternal organism is incapable of responding to the Rh-positive antigen, (*c*) that only in some pregnancies does the antigen enter the maternal circulation or (*d*) that some fetuses are not affected by anti-Rh agglutinins. Each of these factors doubtless operates in some instances, but the third, in view of present knowledge, seems the most important. It is probable that in the majority of women the placental vessels remain intact and no fetal cells gain entrance to the maternal circulation. Only

when a pathologic state permits escape of fetal cells is immunization produced and the way prepared for the subsequent development of erythroblastosis.

2. The titer of maternal anti-Rh agglutinins is not proportionate to the severity of the fetal disease. There seems to be no relationship between (*a*) the severity of erythroblastosis in the fetus or (*b*) the number of affected infants to which a mother has given birth and (*a*) the presence of agglutinins in the maternal circulation, (*b*) the concentration they attain or (*c*) the length of time they persist. It is frequently impossible to demonstrate agglutinins in the blood of women whose infants are affected with the most severe form of the disease, while they may be present in high titer in the blood of women whose infants are only mildly affected. Dockeray and Sacks [103] recently reported testing 61 unselected pregnant women and finding 3 with irregular isoagglutinins of which at least 1 was anti-Rh. All of the women had normal infants. Dockeray and Sacks suggest that the incidence of anti-Rh agglutinins may be much higher than is supposed and postulate that some specific conditions favoring the admission of antibodies to the fetus must be present before erythroblastosis develops. Mollison [104] also reported that weak anti-Rh agglutinins were present during pregnancy in the blood of a woman who gave birth to a normal child with Rh-positive blood. The reason for the lack of correlation between the severity of the disease in the fetus and the concentration of antibodies in the mother's blood is unknown.

3. Some women whose blood is Rh positive give birth to infants stated to have erythroblastosis. The possible reasons for this apparent discrepancy include (1) errors in performing the Rh tests, (2) errors in making the diagnosis of erythroblastosis, (3) initiation of erythroblastosis by some other agglutinogen, (4) initiation of erythroblastosis by some entirely unrelated agent and (5) immunization by a factor in one of the Rh subgroups. It is believed [105] that the first two possibilities function more commonly than the others. There are few published descriptions of infants with conditions diagnosed as erythroblastosis whose mothers had Rh-positive blood, but in those cases for which records are available at least some of the diagnoses seem open to question. In the large series of reports of cases published by Levine, Katzin, Vogel and Burnham [106] the diagnoses were made by scores of physicians, and there is a great chance that errors have been made. The conclusion that the Rh factor has no relation to erythroblastosis which was reached by Gallagher, Danis and Jones [107] because the mothers of a small group of jaundiced infants had Rh-positive blood is unwarranted and seems to have been based on a misconception of erythroblastosis.

However, it appears that in rare instances maternal immunization to other antigens may occur and may produce erythroblastosis. There are a few cases in which the mother seems to have had an increase in $\alpha$ or $\beta$ agglutinins as a result of a pregnancy in which the fetus possessed an A or B antigen that the mother's blood lacked. Boorman, Dodd and Mollison [96] reported titers of 1:3,200 and 1:8,000,000 for anti-B agglutinins in 2 mothers with Rh-positive blood who gave birth to infants with erythroblastosis. They stated that they had observed a titer as high as that shown by the first of these patients in the blood of women delivering normal children. La Vake [108] described a patient who belonged to group O (Rh +) who gave birth to an infant in group B who had erythroblastosis. Five weeks after the delivery the maternal titer of B agglutinins was 1:1,600. By the end of eight months it had fallen to 1:500. The early higher titer was believed due to stimulation by the B agglutinogen in the cells of the fetus. If a positive diagnosis of erythroblastosis can be made in these cases and the possibility of immunization to any other antigen definitely excluded, an injury from $\alpha$ or $\beta$ agglutinins may be presumed.

At least 5 women with infants who had erythroblastosis have been observed whose blood has contained agglutinins different from anti-Rh or any of its previously recognized variants. The first of the serums was mentioned by Levine, Katzin, Vogel and Burnham [106] and by Javert.[109] This serum, which was designated Hr, agglutinated the cells of about 50 per cent of all bloods

103. Dockeray, G. C., and Sacks, H.: Rh Antibodies in the Maternal Circulation Without Clinical Manifestations of Erythroblastosis in the Child, J. Immunol. **48**: 241, 1944.

104. Mollison, P. L.: The Application of Present Knowledge About the Rh Factor, Post-Grad. M. J. **20**:17, 1944.

105. Potter, E. L.: The Rh Factor in Obstetrics, M. Clin. North America **28**:254, 1944.

106. Levine, P.; Katzin, E. M.; Vogel, P., and Burnham, L.: The Antigenicity of the Rh Blood Factor in Transfusion and Pregnancy: Its Role in the Etiology of Erythroblastosis, in Mudd, S., and Thalhimer, W.: Blood Substitutes and Blood Transfusions, Springfield, Ill., Charles C Thomas, Publisher, 1942.

107. Gallagher, F. W.; Danis, P. G., and Jones, L. R.: The Rh Factor in Relation to Jaundice of the Newborn Infant, J. Pediat. **22**:171, 1943.

108. LaVake, R. T.: The Cause of Toxemias of Pregnancy, Journal-Lancet **63**:51, 1943.

109. Javert, C. T.: Further Studies on Erythroblastosis Neonatorum of Obstetric Significance, Am. J. Obst. & Gynec. **43**:921, 1942.

and reacted especially with those which were Rh negative or contained the $Rh_2$ factor. The St serum of Race and Taylor [79] agglutinated all but 20 per cent of bloods and seemed to act on all cells except those of persons whose genotype was $Rh_1Rh_1$. Loutit [81] has suggested that Rh. $Rh_2$, $Rh_0$ (Rh of Wiener, table 5) and Rh″, all of which are agglutinated by anti-St serum, may have in common a partial antigen which is responsible for the reaction to anti-St agglutinins. To which Rh subgroup the patients whose blood contained Hr or St agglutinins belonged has not been reported. It seems apparent, however, that rh, $Rh_2$ $Rh_0$ and Rh″ are all lacking in the patients whose blood contained anti-St agglutinins and that one or a combination of these factors, present in the blood of husband and of the fetus, produced the immunization. A serum believed identical to the St serum has been observed by Diamond [47b] and by Potter and Davidsohn.[56] Levine [110] also recently reported an additional patient whose blood contained anti-Hr agglutinins.

From a study of these rare agglutinins, as well as from the determination of the Rh subgroups which are represented by the parents of infants with erythroblastosis, it seems evident that persons may become immunized to one Rh factor even though possessing another Rh factor in his or her cells. For example, a person whose blood cells contain the factor $Rh_2$ may become immunized to $Rh_1$, Rh′, or $Rh_0$. Although immunization of a person whose blood is Rh negative occurs much more commonly, the response of a person with Rh-positive blood to some Rh factor other than the one present in her own cells may, at times, cause erythroblastosis and is partially responsible for the erythroblastosis in the offspring of women whose blood is Rh negative.

4. The disease frequently becomes more severe immediately after birth than it was during fetal life. If erythroblastosis is caused by the transmission of anti-Rh agglutinins from the mother to the fetus, symptoms would be expected to reach a maximum during intrauterine life and to regress immediately after birth. Anemia, icterus and all signs of hemolysis, however, nearly always become progressively more intense during the first few days of extrauterine existence. A definite explanation of this has not been provided, but there is a strong suggestion in the better survival of transfused Rh-negative blood that agglutinins are still present in the blood of the infant for some time after it is born. On the other hand, almost all infants show destruction of a certain portion of the red cells during the first few days of life, and it is possible that the postnatal destruction observed in erythroblastosis is an abnormal exaggeration of this apparently physiologic process (due to an unknown cause) and not specifically related to hemolysis of cells by anti-Rh agglutinins.

5. $\alpha$ and $\beta$ agglutinins in the maternal blood rarely, if ever, cause fetal erythroblastosis. The question is constantly raised as to why maternal agglutinins which are formed in response to the introduction of the Rh antigen should be capable of passing through the placenta and exerting a harmful influence on the fetal blood cells while $\alpha$ and $\beta$ agglutinins entering the fetal circulation have no effect. Levine [111] has stated repeatedly that he believes this is because A and B substances are present in the tissues and fluids of the body and are therefore capable of absorbing the agglutinins and protecting the blood cells, whereas the Rh antigen is absent from the tissues and the Rh agglutinins consequently can act directly on the blood cells. He also explains the few cases of erythroblastosis in which the mother has Rh-positive blood but is of a different blood group from her husband on the basis that the child is probably a "nonsecretor" [112] and therefore has no A or B antigen anywhere in the body except in the erythrocytes. Although this makes an attractive theory, it appears to be based on two incompletely proved premises. Boorman and Dodd [37] have pointed out that the assumption that occasionally fetal erythroblastosis or some other fatal disease might develop from the effect of $\alpha$ or $\beta$ agglutinins because an infant was a "nonsecretor" may be erroneous. They call attention to the fact that even in the 20 per cent of persons who fail to secrete A or B substances in the saliva, semen or other body fluids the antigen can still be obtained by alcoholic extraction of tissues, thus indicating its presence in various organs, in spite of the absence from aqueous solutions. In the second place, they have also shown that the Rh substance is present in the tissues of the body, in spite of the fact that Levine [36b] and Wiener [36a] assumed it absent because it could not be demonstrated in saliva or seminal fluid.

Although it may be possible that fluid antigen is more potent than tissue antigen in its ability to protect erythrocytes from being destroyed,

110. Levine, P.: Mechanism of the Isoimmunization by the Rh Factor of Red Blood Cells: Standardization of Anti-Rh Serums, Arch. Path. **37**:83 (Feb.) 1944.

111. (*a*) Levine.[94] (*b*) Levine, P.: Genetic and Constitutional Causes of Fetal Death, Collecting Net, 1942, no. 5, p. 17. (*c*) Levine, P.: Erythroblastosis Fetalis and Other Manifestations of Isoimmunization, West. J. Surg. **50**:468, 1942.

112. Schiff, F., and Sasaki, H.: Ueber die Vererbung des serologischen Ausscheidungstypus, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:129, 1932.

there does not seem to be at the present time an entirely adequate explanation of why Rh agglutinins, which are frequently nondemonstrable in maternal blood, should have such a deleterious effect on the fetal cells, while α or β agglutinins, which are commonly present, should have no effect. This fact and the fact that erythroblastosis may progress for several weeks after birth form the principal difficulties in the complete acceptance of the theory that immunization to the Rh factor is the sole cause of the disease.

*Prevention of Erythroblastosis.*—With the fundamental causation of erythroblastosis fairly well established on the basis of maternal immunization, hope is not unwarranted that a method of maternal desensitization may be discovered. This would be of particular value in preventing a repetition of the disease. In most instances the first appearance, even with a method of desensitization, could not be prevented, since the blood of many of the pregnant women does not have demonstrable anti-Rh agglutinins and fetal erythroblastosis (by any means available at present) could not be suspected until after the baby was delivered.

Burnham [113] has suggested giving large amounts of vitamin C to women who have delivered infants with erythroblastosis in the belief that vascular injury (with resultant fetal erythroblastosis) can be expected more commonly in patients with deficiency of vitamin C than in those experiencing no lack. If vitamin C is to be of value, however, it will probably have to be given during the pregnancy prior to the one in which erythroblastosis is first diagnosed. After the disease has developed in one infant, there is little reason to expect that it can be prevented in future pregnancies by the administration of vitamin C. Willson and Potter [114] gave 200 mg. of ascorbic acid and the juice of 3 lemons daily to 2 women during the last five months of pregnancy. Both delivered babies with erythroblastosis, as they had done in previous pregnancies.

Insemination with known Rh-negative sperm from a donor should be one method of permitting a woman with Rh-negative blood to have a normal child. Since both the ova and the sperm are normal in parents with infants suffering from erythroblastosis, each person should be able to have normal children with an appropriate mate. No results of artificial insemination have been reported so far, but Potter and Willson [114] have recently been successful in impregnating a patient with Rh-negative sperm. The outcome of the pregnancy will be watched with much interest, and it is anticipated that a normal child will result. Changing from one mate of the Rh + phenotype to another is of no benefit. Potter [92] has observed 5 women each of whom has had infants with erythroblastosis by 2 husbands. The 3 second husbands who were tested had Rh-positive blood.

The artificial termination of pregnancy by cesarean section as soon as the fetus becomes viable has been recommended, on the assumption that if the fetus can be delivered early enough in the course of pregnancy it may escape being affected by maternal agglutinins.[115] It has also been suggested that the mother's blood be watched closely for the appearance of agglutinins or for a rise in agglutinin titer and that the pregnancy be terminated at the time when agglutinins appear or when the titer suddenly rises.[108] The statement of Rothman and Hopkins [116] that an infant should be delivered by cesarean section with local anesthesia whenever a diagnosis of erythroblastosis has been made on a previous sibling because asphyxia is less apt to occur with abdominal than with vaginal delivery seems open to definite question. Fallon [117] (who stated the conviction that erythroblastosis is due to infection [118]) suggested delivery by cesarean section two to three weeks prior to the expected date of confinement on the assumption that the entrance of bacteria into the fetus from an abnormally permeable placenta during labor could be prevented by abdominal delivery.

If there were no hazard associated with prematurity, early delivery might be an advisable procedure on the supposition that the more prolonged the exposure to anti-Rh agglutinins, the more severe the disease might be. It must be remembered, however, that the fetus is probably affected from early in pregnancy regardless of whether demonstrable agglutinins are present in the maternal circulation and that many infants become much more severely affected immediately after delivery than they were during intrauterine life. Too few cases have as yet been reported to indicate whether early delivery with the con-

113. Burnham, L.: Vitamin C Deficiency as a Possible Factor in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **44**:920, 1942.

114. Willson, J. R., and Potter, E. L.: Unpublished data.

115. Reid, D. E.: Obstetrics: Medical Aspects, New England J. Med. **228**:97, 1943.

116. Rothman, P. E., and Hopkins, H.: The Relationship of Erythroblastosis Fetalis to Intrauterine Asphyxia, Am. J. Obst. & Gynec. **45**:291, 1943.

117. Fallon, M.: Jaundice and Conditions Associated with the Phenomenon, J. Pediat. **23**:721, 1943.

118. Fallon, M.: Classification of the Anemias, Blood Pictures in the Anemias and Anemias in Infants and Children in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3.

sequent discontinuation of direct exposure to anti-Rh agglutinins can outweigh the handicap of prematurity imposed on an infant already suffering from erythroblastosis. Although it is possible that under such circumstances the disease might be of a milder nature, there is no reason to believe that a fetus could be delivered sufficiently early to escape erythroblastosis. At the Chicago Lying-in Hospital, as well as in other clinics, infants have been delivered early by cesarean section only to die subsequently of erythroblastosis despite the administration of blood after birth, and it has been concluded that nothing is to be gained by premature delivery.

*Treatment of Erythroblastosis.*—There is no known form of intrauterine therapy for fetuses suffering from erythroblastosis which in any way will affect the course of the disease. Prior to the discovery of the cause of the condition various procedures had been recommended, almost all directed toward improving the erythrocytic state of the mother or toward stimulating erythropoiesis in the fetus by maternal administration of iron compounds, liver or vitamins. None of these substances appear to have any effect on the fetus.

After birth, the treatment of choice consists of giving the infant transfusions of Rh-negative blood of the appropriate group. Despite the fact that the infant's blood is Rh-positive, Rh-negative blood appears preferable for transfusion.[119] Almost all infants with erythroblastosis show some progression of symptoms after birth, which indicates a continuing exaggerated destruction of erythrocytes after exposure to the intrauterine environment has ceased. If Rh-negative erythrocytes are added to the circulating blood, they should escape destruction, since they contain no antigen to be affected by anti-Rh agglutinins. The total volume of blood in the average newborn infant is between 250[119e] and 350 cc.[120]; therefore, if all of the infant's Rh-positive cells were destroyed it would be possible to replace them with Rh-negative cells by transfusion. Tests of differential agglutination have shown rapid destruction of transfused Rh-positive cells and the normal survival of Rh-negative cells in several infants.[89]

If Rh-negative blood cannot be obtained except from the mother, Wiener and Wexler[119e] have suggested the use of maternal cells which have been washed and suspended in isotonic solution of sodium chloride or normal blood plasma. They further suggested that this might be the method of choice on all occasions, inasmuch as in rare instances it is possible for some factor other than Rh to be responsible for the production of erythroblastosis, and whatever the antigen in the infant responsible for the disease, it would be absent in the mother. If maternal blood cells (washed free of antibodies) were given the baby they would be completely resistant to destruction by antibodies which might have been transmitted to the fetus in utero. It has been shown that agglutinins against the mother's cells are never present in the infant at birth and that consequently maternal cells can be safely given an infant during the first few days of life regardless of differences in blood group.[121]

The administration of Rh-positive blood is preferable to giving no blood at all. In infants with profound anemia an immediate transfusion may be a life-saving measure. Intramuscular or intraperitoneal injection of blood is of practically no value and should not be used.

The time at which to give a transfusion and the amount of blood to be given must be settled for each individual case. An infant with erythroblastosis who has less than 3,000,000 erythrocytes per cubic millimeter of blood at birth should ordinarily be given a transfusion as soon as possible. If the count is below 2,000,000, a delay of a few hours may be fatal. Many infants with counts as low as this at birth will die, regardless of treatment. Irreparable damage (probably from chronic anoxia) seems to have been produced in utero and cannot be cured by the administration of any amount of blood after birth.

Gimson[95b] gave an erythrocyte count of 3,500,000 as a level below which all infants with erythroblastosis should be given transfusions. With counts higher than this immediate transfusion is ordinarily not necessary and frequently not even to be desired. For the first few days determinations of the number of erythrocytes should be repeated at intervals of approximately twelve hours and a transfusion should be given immediately if evidence of a rapid decrease occurs. Even with a gradual decrease the count

119. (*a*) Levine, Burnham, Katzin and Vogel.[81b] (*b*) Boorman, Dodd and Mollison.[47a] (*c*) Mollison.[89] (*d*) Gimson.[95b] (*d*) Rh in Prognosis and Treatment of the Hemolytic Disease of the Newborn, editorial, Brit. M. J. **1**:303, 1943. (*e*) Wiener, A. S., and Wexler, I. B.: Transfusion Therapy of Acute Hemolytic Anemia of the Newborn, Am. J. Clin. Path. **13**:393, 1943. (*f*) Brown, H. R., and Levine, P.: The Rh Factor and Its Importance in Transfusion for the Anemias of Erythroblastosis and Other Causes, J. Pediat. **23**:290, 1943.

120. DeMarsh, Q. B.; Windle, W. F., and Alt, H. L.: Blood Volume of the Newborn Infant in Relation to Early and Late Clamping of the Umbilical Cord, Am. J. Dis. Child. **63**:1123 (June) 1942.

121. Polayes, S. H.; Lederer, M., and Wiener, A. S.: Studies in Isohaemagglutination: The Landsteiner Blood Groups in Mothers and Infants, J. Immunol. **17**:545, 1929.

should probably not be allowed to go much below 3,000,000 before transfusions are given.

English investigators have reported salutory effects from the administration by the drip method over a period of several hours of 120 to 150 cc. of blood. One or at most two transfusions of this amount of Rh-negative blood are ordinarily sufficient.

Most American investigators appear to prefer giving smaller amounts of blood by direct injection and rarely give more than 10 cc. per pound (20 to 22 cc. per kilogram) of body weight at one time. If the cells administered are not destroyed, three or four transfusions of this size should be sufficient for the alleviation of even the most severe conditions.

The normal period of survival of transfused cells appears to be about eighty to one hundred and twenty days.[97] By the end of this time all effect of maternal agglutinins should have been lost and the infant should be manufacturing its own cells. When transfusions do not give the expected increase in circulating erythrocytes, as frequently happens when Rh-positive blood is used, there is often a tendency to give more and more blood. A resultant increase in hemolysis leads to constantly increasing amounts of bilirubin in the blood, and the extremely high levels which may be produced greatly increase the danger of damage to the brain (kernicterus).

Methods of therapy other than transfusion probably have little effect early in the course of the disease; after the infant has survived the first few days of life, administration of iron compounds or liver may help in speeding up the process of complete recovery.

The administration of vitamin K has been suggested [122] as a means of combating the hemorrhagic tendency that is occasionally present. Its use is probably to be recommended, although in most cases hemorrhage appears to be due to hepatic damage and not to a direct lack of vitamin K. The administration of vitamin K frequently fails to prevent hemorrhage.

The addition to the diet of dextrose and preparations containing choline in an attempt to combat the ill effects of possible hepatic damage has been recommended by Danis and Anderson.[123] McKinley [124] attributed a decrease in mortality in infants with erythroblastosis to the administration of calcium gluconate and extract of liver, the latter given intramuscularly.

Splenectomy [125] had been advocated as a method of treatment prior to the discovery of the cause of erythroblastosis. In view of the causation this form of therapy seems to have no justification.

## RELATIONSHIP OF THE RH FACTOR TO OTHER CAUSES OF FETAL AND NEONATAL MORTALITY

Levine [126] postulated maternal immunization to the Rh factor as influential in abortions, malformations and other causes of fetal deaths. The assumption that it might be related to the production of malformations appears to have been based on two studies which indicated that an abnormally high incidence of malformations exists in infants with erythroblastosis.[127] Potter,[92] however, has observed no malformation in over 100 infants and fetuses with erythroblastosis. The mothers of 67 infants and fetuses dying of miscellaneous causes, including malformations, showed only a slightly higher incidence of Rh-negative blood than is found in the general population.[96]

Although women bearing infants with erythroblastosis have a high incidence of abortions, it does not follow that abortions are frequently due to immunization to the Rh factor. Even Levine [93] seems to have concluded that there is probably little relation between the majority of early abortions and the Rh factor. In place of this, however, he has stressed the importance of heterospecific pregnancy—a pregnancy in which the fetus possesses an A or B antigen which is lacking in the mother—and has stated that fetal death is probably due to a reaction between the A or B antigen normal to the fetus and the $\alpha$ or $\beta$ agglutinin transmitted from the mother. He has attempted to show [126c] a higher than normal incidence of heterospecific pregnancies in pregnancies ending in abortion or fetal death of unknown cause and a lower than normal incidence of offspring in group A when the mother is of group O and the father of group A than when the mother is of group A and father of group O.

To date there has been no satisfactory proof that the Rh factor is responsible for any condition other than erythroblastosis or that $\alpha$ or $\beta$

122. Mayman, E. W.: Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, J. Pediat. **17**:806, 1940.

123. (*a*) Danis, P. G.: The Pathogenesis of Jaundice in the Newborn Infant, J. Missouri M. A. **40**:62, 1943. (*b*) Danis, P. G., and Anderson, W. A. D.: Choline Chloride in the Treatment of Icterus Gravis Neonatorum, South. M. J. **35**:1070, 1942.

124. McKinley, H.: Icterus Gravis Neonatorum with Erythroblastosis, Arch. Dis. Childhood **16**:63, 1941.

125. Hardwick, C., and Lloyd, O.: Icterus Gravis Cured by Splenectomy, Lancet **2**:339, 1941.

126. (*a*) Levine.[111b] (*b*) Levine.[111c] (*c*) Levine, P.: Serological Factors as Possible Causes in Spontaneous Abortion, J. Hered. **37**:71, 1943.

127. (*a*) Hawksley and Lightwood.[82b] (*b*) Javert.[109]

agglutinins transmitted to the fetus harm it in any way.

### RELATIONSHIP OF THE RH FACTOR TO REACTIONS TO TRANSFUSIONS

Little more needs to be added about the importance of the Rh factor in relation to the cause and prevention of reactions to transfusions. Immunization to the Rh factor has been shown to be the cause of reactions in approximately 60 persons since its discovery [128] (table 7). From the present concept of the Rh antigen it would appear that under ideal conditions each person prior to receiving a transfusion should have his

TABLE 7.—*Hemolytic Reactions to Transfusions Due to the Presence of Anti-Rh Agglutinins*

| | Patients Having Infants with Erythroblastosis | | | No Erythroblastosis in Offspring or Data Lacking | | | |
|---|---|---|---|---|---|---|---|
| | Total Number | Agglutinins in Blood | Died | Female | Male | Died | Agglutinins in Blood |
| Wiener and Peters [23] | .. | .. | .. | 2 | 1 | 1 | 3 |
| Wiener [28] | .. | .. | .. | 7 | 3 | 2 | 3 |
| Wiener and Forer [36a] | .. | .. | .. | 1 | .. | .. | 1 |
| Wiener et al.[102] | .. | .. | .. | 1 | .. | .. | 1 |
| Wiener * | .. | .. | .. | 2 | .. | .. | 2 |
| Levine et al.[30] | 3 | 2 | 3 | 1 | .. | 1 | 1 |
| Levine et al.[106] | .. | .. | .. | 3(?) | .. | .. | 3 |
| Levine [111c] | 5 | 3 | 5 | .. | .. | .. | .. |
| Schwartz and Levine [98] | .. | .. | .. | 1 | .. | .. | .. |
| Brown and Levine [119f] | .. | .. | .. | 1 | .. | .. | .. |
| Dameshek and Levine [128c] | .. | .. | .. | 1 | .. | .. | 1 |
| Vogel et al.[49] | .. | .. | .. | 4 | 5 | .. | 5 |
| Mayer and Vogel [128d] | .. | .. | .. | 1 | .. | .. | 1 |
| Scott and Conant [29] | .. | .. | .. | 1 | .. | 1 | 1 |
| Koucky [39] | .. | .. | .. | 6 | .. | .. | 4 |
| Mollison [43b] | 1 | .. | 1 | 1 | .. | .. | 1 |
| Mollison [89] | 2 | .. | 2 | .. | .. | .. | .. |
| Boorman et al.[47a] | .. | .. | .. | 2 | 1 | .. | 3 |
| Newton and Tebbutt [52] | .. | .. | .. | 1 | .. | .. | 1 |
| Diamond [46] | 5 | .. | 5 | 5 | 1 | .. | 3 |
| Kariher and Spindler [83c] | 1 | .. | 1 | .. | .. | .. | .. |
| Aagaard [128a] | 2 | .. | 2 | .. | .. | .. | .. |
| Crooks [128b] | .. | .. | .. | 1 | .. | .. | 1 |
| Poncher et al.[128e] | .. | .. | .. | 1 | .. | .. | 1 |
| Adam [140a] | .. | .. | .. | 1 | .. | .. | .. |
| Total | 19 | 5 | 19 | 41 | 11 | 5 | 36 |

* Personal communication.

Rh status determined. If a person has Rh-positive blood, any blood of the appropriate AB group should be tolerated. If the blood of the patient is Rh negative it would seem best to use Rh-negative blood for transfusion if possible. Any person, man or woman, with Rh-negative blood must be considered as potentially capable of becoming immunized to Rh-positive blood. If a single transfusion is given to a man, determination of the Rh factor is unnecessary. It is impossible, however, to be certain that there will never be subsequent need of more blood, and it seems possible that on rare occasions one or two transfusions may produce sufficient immunity to be the cause of a hemolytic reaction many years later. Theoretically no girl or woman with Rh-negative blood should be given Rh-positive cells from birth to the end of reproductive life because of the possibility that they might cause an immunity which would produce erythroblastosis in infants born later.

A large proportion of women with Rh-negative blood who have been pregnant have had a chance to develop anti-Rh agglutinins, and it is extremely important that such women should be given Rh-negative blood. Most important of all is the use of Rh-negative blood for any woman with Rh-negative blood who has given birth to an infant with erythroblastosis. In such cases it is frequently imperative.

If it is impossible to determine whether the blood of the patient or of the donor is Rh negative, careful cross matching by the incubation-centrifugation technic followed by the use of Wiener's "biologic test" is essential if blood must be given to a woman who has had an infant with erythroblastosis.

Of increasing importance is the determination of the Rh status and the giving of Rh-negative blood by transfusion to persons with Rh-negative blood if the patient is (1) a boy or man apparently in need of a single transfusion, (2) a boy or man apparently in need of multiple transfusions, (3) a girl or woman who has never been pregnant, (4) a woman who has been pregnant but has had no abortions or stillbirths and has lost no infant by neonatal death, (5) a woman who has had an abortion or a stillbirth or who has lost an infant by a neonatal death not diagnosed as due to erythroblastosis, (6) a woman who has given birth to an infant with erythroblastosis but whose blood shows no anti-Rh agglutinins, (7) a woman who has had an infant with erythroblastosis and whose blood shows anti-Rh agglutinins or a man whose blood contains agglutinins as a result of previous transfusions. Persons in group 6 should never under any circumstances be given Rh-positive blood and those in group 5 should not receive it if it can possibly be avoided.

### LABORATORY TESTS FOR RH AGGLUTINOGEN AND AGGLUTININ

*Testing for the Rh Factor.*—Two methods for the determination of the presence or absence

128. (*a*) Aagaard, G. N.: Transfusion Reactions and Erythroblastosis Foetalis Caused by the Rh Factor, Minnesota Med. **25**:267, 1942. (*b*) Crooks, P. E.: Blood Transfusion Reaction Due to Intragroup Incompatibility, Am. J. Obst. & Gynec. **44**:121, 1942. (*c*) Dameshek, W., and Levine, P.: Isoimmunization with the Rh Factor in Acquired Hemolytic Anemia, New England J. Med. **228**:641, 1943. (*d*) Mayer, M. D., and Vogel, P.: Intra-group Hemolytic Transfusion Reaction Due to the Rh Agglutinogen as a Result of the Isoimmunization in Pregnancy, J. Mt. Sinai Hosp. **8**:300, 1941. (*e*) Poncher, H. G.; Weir, H. F., and Davidsohn, I.: Observations on Hemolysin in Acute Hemolytic Anemia, J. Pediat. **22**:387, 1943.

of the Rh factor have been described. The choice of method depends largely on whether the source of the testing serum is animal or human, although the two methods may be used interchangeably or combined. Since agglutination is rarely intense, the slide technic such as that frequently used for AB grouping is not ordinarily satisfactory. Tests for the Rh factor are more difficult than those for A and B substances, and the performance and interpretation require more experience.[129]

HUMAN SERUM: One to two drops of a 2 per cent suspension of the red blood cells in isotonic solution of sodium chloride is placed in a test tube of 7 mm. bore, and an equal amount of testing serum is added. The mixture is lightly shaken and placed in an incubator or waterbath at 37 C. for one hour. It is then centrifuged at 500 revolutions per minute for one minute and again lightly shaken. If agglutination is not visible to the unaided eye, the mixture in the tube is examined with a hand lens or the tube is placed on the mirror and examined under the low power of a microscope. If neither of these examinations is conclusive, a drop of the suspension is placed on a slide and examined microscopically. Care must be taken not to shake the suspension too vigorously or agglutinated cells may be separated. When reactions are weak, it may be difficult to tell whether true agglutination or rouleau formation is responsible for the appearance. The use of serum of sufficiently high titer to permit dilution reduces the likelihood of rouleau formation.[47a]

Because of the variability in the agglutinins in different human serums it is advisable for one to perform the tests with not less than three different serums before a diagnosis is made.[130] Known Rh-positive and Rh-negative cells should be set up simultaneously with the same serums to act as controls. Clotted whole blood or concentrated citrated blood if kept in a refrigerator may be used satisfactorily for a period up to two weeks if fresh suspensions of cells are made at the time of testing.

Several investigators[131] recommend washing the cells before making the suspension. The suspension should always be freshly prepared immediately before making the test. Suspensions with more than 2 per cent concentration of blood sediment are especially apt to give false negative reactions, while those with less than 2 per cent commonly give inconclusive results.

Certain serums have been described which are more active at refrigerator or room temperature than at 37 C.[23] The majority, however, react most favorably at 37 C. and show little or no agglutination at lower temperatures. Fisk and Foord[68] stated that lower dilutions of potent serum will frequently give the same reaction at room temperature that higher dilutions will give at 37 C. The use of higher temperatures thus conserves testing material. The optimum dilution and temperature for activity for each serum should be determined prior to use, and the tests should be performed under correct conditions.[132]

ANIMAL SERUM: One to two drops of a 2 per cent suspension of cells and 2 drops of serum are placed in a 7 mm. bore test tube, as in testing with human serum. Animal serum in general reacts as well at 20 C. as at 37 C., so the tubes may be kept at room temperature. After thirty to sixty minutes the sediment in the bottom of the tube is examined with the aid of a hand lens. Negatively reacting blood shows a compact circular sediment with a smooth edge, while positively reacting blood has a loose wrinkled sediment with a serrated border or a peripheral granular deposit.[57] After the first examination the mixture is shaken and reexamined an hour later, when the sediment has reformed. The tubes are then gently shaken and the suspension examined microscopically; the samples which react negatively are mostly homogeneous, while those which react positively show various degrees of agglutination. It is stated that at times the clumping is weak in spite of the presence of a positive pattern of sedimentation. Landsteiner and Wiener[57] commented that it may be necessary to repeat the test several times before arriving at a definite conclusion. Bloods of known negative and positive reactions should be set up with each unknown.

It would appear that the use of animal serum requires more experience and technical ability and is more susceptible to false diagnosis than the use of human serum.

The only investigators to report the satisfactory use of a slide technic are Simmons, Graydon, Jakobowicz and Bryce.[133] They kept mixtures of cells and serum on slides in moist chambers at 20 C. and at 37 C. and obtained agglutination of Rh-positive cells in fifteen to

129. Thalhimer, W.: Blood Typing and Criteria for Blood-Typing Serums, J. Pediat. **23**:715, 1943.

130. (*a*) Potter, Davidsohn and Crunden.[96a] (*b*) Taylor, G. L.: Tests for the Rh Factor and Its Antibody, Proc. Roy. Soc. Med. **36**:225, 1943.

131. (*a*) Wiener.[60] (*b*) Fisk and Foord.[68] (*c*) McIvor, B. C., and Lucia, S. P.: Rapid Method for Obtaining Anti-Rh Serum from Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **52**:293, 1943.

132. (*a*) Thalhimer.[129] (*b*) McIvor and Lucia.[131c]

133. Simmons, R. T.; Graydon, J. J.; Jakobowicz, R., and Bryce, L. M.: The Rh Factor: Its Incidence in a Series of Victorian Red Cross Donors, M. J. Australia **2**:496, 1943.

sixty minutes. The test tube technic gave complete corroboration whenever used. Occasionally serums have been found in other laboratories which also gave rapid agglutination on slides,[47b] but with the majority of the serums which are available it is necessary to use a more sensitive technic.

*Determining the Presence of Anti-Rh Agglutinins.*—Serum to be tested for the presence of anti-Rh agglutinins is used in place of known serum and the tests carried out as described for human or animal serum depending on the source of serum and the preference of the investigator. It is recommended that the serum be tested with a minimum of ten suspensions of cells, of which at least two contain known Rh-positive cells and two Rh-negative cells. If the serum agglutinates the known Rh-positive cells and the majority of the unknown cells and fails to agglutinate the known Rh-negative cells, it can be assumed that the agglutinin present is anti-Rh. Boorman, Dodd and Mollison[47a] have stated that it is advisable to test the serum against the patient's own cells to be certain that abnormally powerful autoagglutinins are not responsible for the clumping of cells. If autoagglutinins are present, they may be partially removed by leaving the serum in contact with its own clot at refrigerator temperature and then removing the serum while it is still cold.

If fresh serum is used, Wiener[60] and Taylor[130b] have recommended its inactivation at 56 C. for ten to twenty minutes in order to destroy an inhibitory substance which is occasionally present.

Taylor and his associates[134] have shown that at times there is a noticeable zone phenomenon. Serum which completely failed to agglutinate cells when used full strength in some instances gave a strong reaction when diluted. Almost all serums examined gave stronger reactions at dilutions of 1:4 and 1:8 than in the undiluted state. Taylor and his associates recommended that all tests for the presence of anti-Rh agglutinins should be run in multiple dilutions before a decision is reached that agglutinins are absent.

Great variation in the reactivity of the red blood cells of different persons has been noted, some reacting poorly (but positively) to all serums and others giving strong agglutination with some and weak agglutination with others. Cells known to react well with most serums should be used as controls in testing for the Rh factor and for the presence of agglutinins. Wiener's work on the variety of Rh types explains much of the variation in reaction. He has shown a definite relationship between the degree of agglutination and the subgroup to which the Rh factor in the cells belongs.

When attempts are made to determine changes in the titer of anti-Rh agglutinins, care must be taken to use blood cells from the same person or cells known to be of the same Rh type for all titrations. A difference in the ability of the cells to react may otherwise give a false impression of a change in the concentration of agglutinins.

Cross matching prior to all transfusions should ideally be carried out by the method described for the determination of the Rh factor, using the patient's serum and the prospective donor's cells. Control tests should always be performed.[86] The work of Taylor and his associates indicates that cross matching should also be set up with at least four dilutions, 1:1, 1:2, 1:4 and 1:8. The test tube incubation method is especially important if the patient is known to have Rh-negative blood or has had a previous transfusion or pregnancy.

*Preparation of Testing Serum for Rh Determinations.*—ANIMAL SERUM: In the original discovery of the Rh factor Landsteiner and Wiener[25] used serum which was obtained from rabbits that had received a course of intravenous injections of blood from the Rhesus monkey. They subsequently demonstrated that guinea pigs gave a more satisfactory response than rabbits. After beginning with two injections[57] of washed cells from 2 cc. of blood at five day intervals, they finally increased the number of injections to five,[135] using the same amount of blood each time. The animals were bled one week after the last injection, and satisfactory serums were pooled.

Although various minor modifications have been suggested by other investigators, no entirely satisfactory method of producing animal serum has yet been devised. Guinea pigs react somewhat more favorably than rabbits, but it is rare to get a serum which is satisfactory from more than half of the animals given injections, and often serum from only 2 or 3 can be used.[136]

The original investigators recommend that before use pooled guinea pig serum that is preserved with 1:1,000 merthiolate be inactivated

134. (*a*) Taylor[130b] (*b*) Taylor G. L.; Race, R. R.; Prior, A. M., and Ikin, E. U.: Optimal Proportions of Antigen and Antibody in Tests for Rh Antibodies, Brit. M. J. **2**:572, 1942.

135. Landsteiner, K., and Wiener, A. S.: Tests for the Rh Factor with Guinea Pig Immune Serum, Proc. Soc. Exper. Biol. & Med. **51**:313, 1942.

136. (*a*) Hoare, E. D.: Occurrence of the Rh Antigen in the Population: Notes on Five Cases of Erythroblastosis Foetalis, Brit. M. J. **2**:297, 1943. (*b*) Dahr, P.: Die bisherigen Untersuchungen ueber die Vererbung der neuen agglutinablen Blutkörpercheneigenschaft "Rh," abstracted, Bull. War Med. **3**:448, 1943.

at 56 C. for one hour and serum that is fresh be diluted ten times with isotonic solution of sodium chloride and adsorbed for one hour at room temperature with one-tenth volume of washed blood sediment containing equal parts of $A_1$ and B blood. It is stated to make no difference whether the blood used for adsorption is Rh positive or Rh negative. Further dilution of the adsorbed serum to 1:4 at the time of use seems to enhance its ability to differentiate Rh-positive from Rh-negative cells.

Gallagher and Jones [137] prepared guinea pig serum for use by diluting one volume of serum with three volumes of isotonic solution of sodium chloride and adding one volume of packed, washed M Rh-negative erythrocytes of any group with respect to factors A and B. They found that if the serum was not inactivated prior to use the cells tested were apt to become hemolyzed instead of agglutinated. They [137] also reported the successful production of anti-Rh serum by the injection of human cells instead of monkey cells into guinea pigs. Various doses of O MN Rh-positive cells were given during a period of three months. The serum after adsorption with O MN Rh-negative cells differentiated sharply between human Rh-positive and Rh-negative cells.

Fisk and Foord [68] found that guinea pig serum differentiated much more sharply between Rh-positive and Rh-negative cells and could be used in greater dilutions if it was adsorbed once in a dilution of 1:10 with a half volume of Rh-negative washed blood sediment. A 1:20 dilution of the serum was used for the final tests.

HUMAN SERUM: When the presence of anti-Rh agglutinins of sufficiently high titer in serum from any patient has been established, the serum, after appropriate treatment, may be used as testing material. Unless the serum is obtained from a patient of group AB or used only to test persons of the same blood group, isoagglutinins must be removed by the addition of boiled saliva prepared according to the method outlined by Wiener,[138] or by the addition of Witebsky's [139] purified A and B substances. The serum should be inactivated by heating for ten to twenty minutes at 56 C. if it is used fresh. Before its suitability is established its reaction to a large number of samples of human cells, preferably at least one hundred, must be known. The serums that are most desirable agglutinate 85 per cent of all cells, and their reactions in general parallel those given by animal serum. Serums giving other percentages of positive reactions are valuable for demonstrating the presence of variants of the Rh antigen. Several different serums should be used whenever cells are to be tested; at least one should give positive reactions with 85 per cent of unselected samples tested.

The majority of women whose blood contains agglutinins have an antibody titer so low that the serum cannot be used for testing. It is estimated that suitable serum can be obtained from only about 1 of 4,000 pregnant women. A method has recently been developed, however, which promises to make more serum available. Although a relatively small yield is obtained, serum which previously was of no value may be converted into material valuable for testing by concentration of the antibody-bearing globulin fraction.

## SUMMARY

In the short time that has elapsed since the discovery of the Rh factor and the establishment of its relation to erythroblastosis and to reactions to transfusions, information concerning it has become remarkably general. In addition to the investigative work that has been reported, numerous general reviews have been published by Levine and by other interested persons.[140]

137. Gallagher, F. W., and Jones, L. R.: Production of Rh Antiserums by Inoculation of Guinea Pigs with Human Erythrocytes, Proc. Soc. Exper. Biol. & Med. **43**:119, 1943.

138. (*a*) Wiener and Forer.[36] (*b*) Wiener.[60]

139. (*a*) Witebsky, E.; Klendshoj, N., and Swanson, P.: Preparation and Transfusion of Safe Universal Blood, J. A. M. A. **116**:2654 (June 14) 1941. (*b*) Witebsky, E.; Klendshoj, N. C., and Swanson, P.: Neutralization of Isoagglutinins Anti-A and Anti-B in Blood by Means of the Addition of the Isolated Blood Group Specific Substances, in Mudd, S., and Thalhimer, W.: Blood Substitutes and Blood Transfusions, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 327.

140. (*a*) Adam, G. S.: The Rh Factor and Its Application to Obstetric Practice, M. J. Australia **1**: 507, 1943. (*b*) Brewer, H. F.: A Note on the Rh Factor and Its Significance, St. Barth. Hosp. J., War Ed. **4**:48, 1943. (*c*) Bethell, F. H.; Sturgis, C. C.; Hettig, R. A., and Mallery, O. T., Jr.: Blood: A Review of the Recent Literature, Arch. Int. Med. **71**: 854 (June) 1943. (*d*) Bryce, L. M., and Jakobowicz, R.: Uncommon or Anomalous Agglutination Reactions in Human Blood, Roy. Melbourne Hosp. Clin. Rep. **13**:50, 1942. (*e*) Dameshek, W.; Greenwalt, T. J., and Tat, R. J.: Erythroblastosis Foetalis (Acute Hemolytic Anemia of the Newborn), Am. J. Dis. Child. **65**:571 (April) 1943. (*f*) Falkenstein, A. P.: Significance of the Rh Factor in Intragroup Transfusion Reactions and Erythroblastosis Fetalis, Ohio State M. J. **39**:644, 1943. (*g*) Leonard, T. A.: Erythroblastosis Foetalis and Its Relationship to Transfusion Reactions and Accidents, Wisconsin M. J. **42**:1034, 1943. (*h*) Lindsey, D.: Autoagglutination, Cold Agglutination, Pseudoagglutination and the Rh Factor, New Orleans M. & S. J. **95**:382, 1943. (*i*) Newerla, G. J.: Erythroblastosis Foetalis: Report of a Case, New England J. Med. **229**:576, 1943. (*j*) Porter, J. E.: The Significance of the Rh Factor of the Blood, J. Maine M. A. **34**:63, 1943. (*k*) Raimondi, D.:

*(Footnote continued on next page)*

There seems little doubt that in most instances the fundamental cause of erythroblastosis is the immunization of a mother with Rh-negative blood by the Rh-positive blood of the fetus. An added factor is involved, the nature of which has not yet been determined. It is generally presumed to be an abnormality in the placenta which permits the escape of fetal cells. Haldane [74] postulated that a gene causing abnormal placental permeability must be present in addition to the one determining the Rh-negative state before erythroblastosis occurs. Wiener stated that the capacity to become sensitized is constitutional [102] and is on a definite genetic basis as evidenced by the inheritance of certain allergic diseases.[141] Potter [92] questioned over 50 women who had given birth to infants with erythroblastosis concerning the occurrence of hay fever, asthma and allergic reactions to foods, drugs or other substances and found that less than 15 per cent had any allergic manifestations. Reproductive histories of the mothers and maternal grandmothers of these 50 women, with 1 exception, failed to show any evidence that erythroblastosis might have been present in any of their children. One patient (the one with whom this particular investigation started) stated that she was the fourth child and that her mother subsequently had had 5 miscarriages. The cause given was the short interval between pregnancies. This was the only case in which there was any suggestion that mother and daughter may both have given birth to infants with erythroblastosis. Although the majority of the mothers of infants with erythroblastosis had sisters with children there was no evidence suggesting the possibility of erythroblastosis in any of their offspring. Taylor, Cappell and McFarlane [51] and others have observed that there are fewer normal siblings born after an infant with erythroblastosis than would be expected if the incidence of heterozygosity in fathers of such infants were similar to that in the general population. This has suggested that erythroblastosis is more apt to occur when the father has two Rh-positive genes than when he has only one. By the use of their St serum Taylor and Race have been able to show that this is true.[142] Of 38 fathers of infants with erythroblastosis only 5 were of the genotype $Rh_1rh$, while of 38 phenotypically Rh-positive men selected at random 15 were of the genotype $Rh_1rh$.

Although it is impossible to say why an immunity to the Rh antigen is developed in certain women with Rh-negative blood and not in others, all of the observations which have been made by the present author and all of the data thus far published show no exception to the following facts: 1. When a patient once has an offspring with erythroblastosis caused by immunization to the Rh factor, all subsequent children are affected unless they have Rh-negative blood. 2. Fertilization by Rh-positive sperm will produce a child who will have erythroblastosis if any previous sibling has had the disease. 3. An infant with Rh-negative blood may escape the disease in an environment that produces it in a twin with Rh-positive blood. 4. There is no evidence of direct inheritance of erythroblastosis. 5. There is no maternal abnormality of any kind which is constantly associated with this condition. 6. If a woman has given birth to an infant with erythroblastosis, a hemolytic reaction will usually develop if she is given a transfusion of Rh-positive blood.

Chicago Lying-in Hospital.

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# Abstracts from Current Literature

## Biochemistry; Bacteriology, and Pathology

ELECTRON MICROSCOPE STUDIES OF BACTERIAL VIRUSES. S. E. LURIA, M. DELBRUCK and T. F. ANDERSON, J. Bact. **46**:57 (July) 1943.

The electron microscope, recently introduced as a ool for biologic research, has been applied with great nthusiasm to the study of animal and plant viruses. he authors have investigated 4 strains of bacterial iruses. In all cases the particles of virus could be dentified on the micrographs. Three of these strains how "sperm-shaped" particles consisting of a head and tail. The micrographs of 2 viruses which act on e same strain of Escherichia coli demonstrated the dsorption of virus on the host and, after the predicted ime, the lysis of the host with the liberation of virus articles of the infecting type. Along with the virus articles, the lysing cells shed protoplasmic material f uniform granular structure, and the size of these ranules was much smaller than that of the particles f virus. For a discussion of the bearing of these re-ults on the problems of the nature of viruses the riginal paper should be consulted.

STOESSER, Minneapolis.

ALMONELLA ENTERITIDIS: EXPERIMENTAL TRANSMISSION BY THE ROCKY MOUNTAIN WOOD TICK, DERMACENTOR ANDERSONI STILES. R. R. PARKER and EDWARD A. STEINHAUS, Pub. Health Rep. **58**: 1010 (July 2) 1943.

The authors present data to show that when Salmonella enteritidis is ingested by the Rocky Mountain ood tick the bacterium survives in the tick and can e transmitted by it. This may occur as long as thirty-ve days after a meal of infective blood. This is the econd bacterium shown to be transmissible by Dermacentor andersoni. The first was Pasteurella tularensis.

SANFORD, Chicago.

## Metabolism; Infant Feeding; Milk and Other Foods

URTHER STUDIES ON THE SYMPTOMS OF MANGANESE DEFICIENCY IN THE RAT AND MOUSE. MAURICE E. SHILS and E. V. MCCOLLUM, J. Nutrition **26**:1 (July) 1943.

The authors present a new solid basal diet which extremely low in manganese. Female rats started n the manganese-low diet at weaning produced non-ble young, owing to deficiency of manganese. The trus cycle was not disturbed in the first generation females on this deficient diet. The same results re noted in mice. Growth was not decreased in the ficient rats of the first generation on the basal diet. hen the offspring, particularly the male offspring, stock females which had been placed on the deficient et late in pregnancy were kept on the low-manganese et they were inferior in growth to littermates which re given manganese. An increase in the calcium d phosphorus contents of the basal diet produced a crease in growth of first generation males. For timum growth, manganese is essential. The deficient les were sterile. Loss of both equilibrium and ordination was noted in the young rats on the manganese-deficient diet. A definite decrease in activity of arginase in the livers of the deficient rats was noted. The symptoms of manganese deficiency, production of inferior young, poor growth of the female and sterility and poor growth of the male could be eliminated by the addition of manganese to the diet.

FREDEEN, Kansas City, Mo.

THE AMINO ACIDS REQUIRED FOR GROWTH IN MICE AND THE AVAILABILITY OF THEIR OPTICAL ISOMERS. CLIFFORD D. BAUER and CLARENCE P. BERG, J. Nutrition **26**:51 (July) 1943.

In mice fed mixtures of twenty purified amino acids as the source of protein nitrogen moderate growth was obtained. Only the natural forms of valine, leucine, isoleucine and threonine could be utilized for this purpose and both optical forms of methionine and phenylalanine. The elimination of arginine from the diet did not retard the rate of growth; apparently the mouse is able to synthesize arginine at a fairly rapid rate. When the source of protein nitrogen was limited to the seven amino acids already mentioned (valine, leucine, isoleucine, threonine, methionine, phenylalanine and arginine) plus lysine, tryptophan and histidine, slow growth occurred.

FREDEEN, Kansas City, Mo.

EFFECT OF LEAD ABSORPTION ON BLOOD CALCIUM. WENDELL V. JENRETTE, Pub. Health Rep. **58**:1001 (July 2) 1943.

Investigation of the content of calcium in the blood serum of animals ingesting large amounts of lead as well as of animals receiving smaller doses over a longer period of time at different levels of intake of calcium indicates that absorption of lead does not appreciably affect the level of calcium in the blood.

SANFORD, Chicago. [AUTHOR'S SUMMARY]

REPORT ABOUT NUTRITION IN ECUADOR. CARLOS ANDRADE MARÍN, Bol. Inst. internac. am. de protec. a la infancia **17**:37 (July) 1943.

The author concludes that the council of the International American Institute for the Protection of Childhood might recommend to the government of Ecuador these important measures for improving the nutritional status of the people: (1) creation of a national institute of nutrition or at least appointment of a special committee as suggested in the third resolution of the eighth Pan-American Congress, and (2) changes in the policy of production and consumption of milk in order to provide pure and guaranteed milk for children.

EDITOR'S SUMMARY.

REPORT ABOUT NUTRITION IN URUGUAY. JUAN ANTONIO COLLAZO, Bol. Inst. internac. am. de protec. a la infancia **17**:125 (July) 1943.

The nutrition of children begins in the prenatal period, when the expectant mother should be provided with abundant nutrient elements. In Uruguay, as in nearly all the world, it is necessary to encourage greater consumption of milk, citrus fruits, fish, vegetables and meat by children of different ages. The statistics available are insufficient and incomplete, but it may be noticed that in the city and to a greater

extent in rural areas the average diet is lacking in protective agents such as vitamins, minerals and specific amino acids.

Almost all of the national wealth is dedicated to the commercial production of foods of the highest biologic value, proteins from animal source, vitamins, citrus fruit, milk and grain.

Development of the potential wealth, commercially unexploited, of the fishing grounds which are so abundant along the shores of Uruguay and scientific improvement of dairying and of the citrus industries in this period of emergency would allow increased exportation of meat. These desirable advances would require capital stock and inter-American credit.

Statistics show an apparently high consumption of "protective" and "essential" foods by the Uruguayan population as well as by the Argentine population, but it is evident that only in the cities of Montevideo and Buenos Aires is the population able to eat well; in the rest of the country the lack of protective and essential foods produces a state of nutritional deficiency, with subsequent danger to public health and detriment to the efficiency of the persons concerned.

By a wise policy for national nutrition, such as those recently planned at the National Conference on Nutrition for Defense (Washington, 1941), at the American Conference of Business and Productive Associations (Montevideo, 1941) and at the Third International Conference on Nutrition, held under the auspices of the League of Nations (Buenos Aires, 1939), the nutrition of the people of the Americas can be improved so as to change them into a healthy, prolific and brave group of people, able to be efficient at work and to defend the rights of liberty.

In Uruguay the families of moderate income could be the best fed in the world, for there is no other country so well provided with the foods specified by modern nutritional science. EDITOR'S SUMMARY.

PRESENT CONDITION OF THE PROBLEM OF NUTRITION IN THE AMERICAN COUNTRIES: STATEMENT OF THE PROBLEM IN VENEZUELA. Bol. Inst. internac. am. de protec. a la infancia, **17**:139 (July) 1943.

In Venezuela the present deficiency in nutrition is related to the traditional habits of the people and to the low income of the working class and the rural group; both of these factors contribute to the excessive consumption of carbohydrates and to the deficiency of proteins and vitamins in the diet. To get an adequate nutritional allowance for his family the Venezuelan worker has to spend 60 to 75 per cent of his salary for food. Several studies made in Caracas have demonstrated that 78.32 per cent of the dystrophies in children are due to lack of food.

Some of the measures already adopted by the government for the betterment of the nutrition of the population are the following: (*a*) Distribution of free milk to children and mothers attending the clinics for the care of children; in 1941 the ministry of public health and social assistance distributed 507,350 liters of milk; (*b*) creation of school lunchrooms; at present there are forty of them throughout the country the average meal served provides 1,223 calories and 70 Gm. of protein, 440 mg. of calcium and 733 mg. of phosphorus, at the cost of 0.50 bolívares per capita per day; (*c*) establishment and support of two popular restaurants; (*d*) initiation of measures to insure a higher basic level of wages; (*e*) extensive protection of agriculture and cattle breeding; (*f*) enactment, in the year 1941, of the social insurance law (providing benefits for diseases and maternity), and (*g*) beginning of an intensive educational program.

FROM THE EDITOR'S SUMMARY.

## Vitamins; Avitaminoses

EFFECTS PRODUCED BY VITAMIN D ON ENERGY, APPETITE AND OESTROUS CYCLES OF RATS KEPT ON AN EXCLUSIVE DIET OF YELLOW CORN. CURT P. RICHTER and KATHERINE K. RICE, Am. J. Physiol. **139**:693 (Sept.) 1943.

The decreased activity, poor appetite and constant state of dioestrus produced in rats by an exclusive diet of yellow corn are all corrected by giving the animals access to a solution of pure vitamin $D_3$. Ultraviolet irradiation of animals fed yellow corn has a similar corrective effect but to a smaller extent.

Both vitamin A acetate and a distillate of cod liver oil without any vitamin A or D were essentially without effect on the nutritive condition of rats maintained on the yellow corn diet for one hundred days. Therefore, it is concluded that the value of cod liver oil as a supplement to an exclusive diet of yellow corn is, in all probability, due to the vitamin D content of the fish oil.

Attention is called to the close similarity between the symptoms of rats on an exclusive diet of yellow corn and those of hypophysectomized rats, and the possibility was considered that vitamin D might achieve its effect indirectly through stimulation of the anterior lobe of the hypophysis. FROM THE AUTHORS' SUMMARY.

VITAMIN A LEVELS IN MATERNAL AND FETAL BLOOD PLASMA. JANE NICHOLLS BYRN and N. J. EASTMAN, Bull. Johns Hopkins Hosp. **73**:132 (Aug.) 1943.

Samples of blood from the umbilical cords of infants showed substantial amounts of vitamin A in the plasma. The average value was 91.3 U. S. P. units per hundred cubic centimeters, compared with an average maternal level, taken a few hours before delivery, of 106.3 U. S. P. units. High doses of vitamin A fed to 15 women in labor failed to raise the levels in the infants above those in untreated controls.

LYTTLE, New York.

THE CONCENTRATION OF VITAMIN A IN THE BLOOD PLASMA DURING PREGNANCY. OSCAR BODANSKY, J. M. LEWIS and MICHAEL C. C. LILLIENFELD, J. Clin. Investigation **22**:643 (Sept.) 1943.

The mean concentration of vitamin A in the plasma of 70 women who were six months pregnant or less was 105.4 U. S. P. units per hundred cubic centimeters (standard deviation of 23.2 units). The mean value for 62 women in the third trimester of pregnancy was 91 units per hundred cubic centimeters (standard deviation of 26.2 units) and hence significantly lower than the mean value during the first two trimesters.

The mean value of the plasma carotene during the sixth, seventh and eighth months (145.9 micrograms per hundred cubic centimeters) was significantly higher than during the first five months (111.9 micrograms per hundred cubic centimeters).

The decrease in the concentration of vitamin A in the plasma during the third trimester is probably due to storage in the fetal liver and utilization by the fetal tissues. Other possible mechanisms are discussed.

AUTHORS' SUMMARY.

HE EFFECT OF CONCENTRATION ON THE ABSORPTION OF VITAMIN A. A. GEORGE REIFMAN, LOIS F. HALLMAN and HARRY J. DEUEL JR., J. Nutrition **26**:33 (July) 1943.

The rate of absorption of vitamin A in rats was und to be proportional to the concentration of the tamin in the administered material. No relationship tween the rates of absorption of neutral fat and tamin A was noted. Vitamin A apparently was not stroyed by contact with intestinal bacteria for a riod of three hours. FREDEEN, Kansas City, Mo.

OTIN CONTENT OF MEAT AND MEAT PRODUCTS. B. S. SCHWEIGERT, E. NIELSEN, J. M. MCINTIRE and C. A. ELVEHJEM, J. Nutrition **26**:65 (July) 1943.

Of the meats and meat products tested, kidney and er were the richest sources of biotin, as determined the effect on the growth of Lactobacillus casei. od sources were heart, pancreas and dark and light icken meat. Beef spleen, lung, brain and tongue had out the same amount of biotin in millimicrograms per am of fresh tissue as did lamb, beef, veal and pork uscle. Pork loins and hams averaged 50 millimicro-ams of biotin per gram of fresh tissue. About 77 r cent of the biotin was retained in the meat alone er cooking and about 80 per cent in the meat plus ippings. FREDEEN, Kansas City, Mo.

HE RETENTION OF VITAMINS IN MEATS DURING STORAGE, CURING AND COOKING. B. S. SCHWEIGERT, J. M. MCINTIRE and C. A. ELVEHJEM, J. Nutrition **26**:73 (July) 1943.

The contents of thiamine, nicotinic acid and riboflavin fresh, fresh stored and cured hams before and after oking were determined. The thiamine and nicotinic d retained during storage averaged 92 per cent, and riboflavin retained was 85 per cent. The amounts ained after curing were thiamine 73 per cent, nico-ic acid 84 per cent and riboflavin 92 per cent. After sting, in the meat alone the average retention was amine 58 per cent, nicotinic acid 79 per cent and oflavin 74 per cent; after frying, thiamine 86 per t, nicotinic acid 85 per cent and riboflavin 77 per t. The total retention in the meat plus drippings r roasting averaged 70 per cent for thiamine, 96 per t for nicotinic acid and 84 per cent for riboflavin; r frying, thiamine 92 per cent, nicotinic acid 96 per t and riboflavin 86 per cent. The over-all retention the vitamins from fresh stored to cured fried samples eed with the vitamin retention during curing and ing. A higher retention of thiamine in the meat ne was found after frying, as compared with roast-, braising and broiling.

FREDEEN, Kansas City, Mo.

TAMIN K AND PROTHROMBIN LEVELS WITH SPECIAL REFERENCE TO THE INFLUENCE OF AGE. F. W. STAMLER, R. T. TIDRICK and E. D. WARNER, J. Nutrition **26**:95 (July) 1943.

To maintain the normal level of prothrombin, young ite leghorn chicks required 1 to 2 micrograms of ethyl-1,4-naphthoquinone per day. About one twen-h of this amount was necessary to maintain sufficient hrombin in the blood to protect the animal from morrhagic manifestations. As the chick increased age, despite the fact that the body weight increased eralfold within a few weeks, no increase in the ount of vitamin K was required. The data suggested that a large portion of the vitamin requirement of the growing chick was associated with the increase in size.

FREDEEN, Kansas City, Mo.

THE EFFECT OF COOKING WITH AND WITHOUT SODIUM BICARBONATE ON THE THIAMINE, RIBOFLAVIN AND ASCORBIC ACID CONTENT OF PEAS. CORNELIA H. JOHNSTON, LOUISE SCHAUER, SAM RAPAPORT AND HARRY J. DEUEL JR., J. Nutrition **26**:227 (Sept.) 1943.

The addition of sodium bicarbonate to the water decreased the time necessary for the cooking of peas, both fresh and frozen. Approximately 80 per cent of the thiamine, 65 per cent of the riboflavin and 45 to 60 per cent of the ascorbic acid was retained in the peas after cooking. There were no differences from the addition of sodium bicarbonate to the cooking water. When the vitamin content of the cooked peas was added to that of the cooking water, the recovery of these three vitamins was found to be practically complete. The destruction of vitamin C by the cooking process amounted to between 15 and 20 per cent in the frozen peas, and this was not influenced by the method used. With overcooking, to the extent that the peas started to disintegrate, the losses of thiamine from both fresh and frozen peas were considerably greater and the recovery was much less. Under these conditions the destructive effect of sodium bicarbonate was somewhat greater. FREDEEN, Kansas City, Mo.

THE EFFECT OF COMMERCIAL CLARIFICATION ON THE VITAMIN CONTENT OF HONEY. M. H. HAYDAK, L. S. PALMER, M. C. TANQUARY and A. E. VIVINO, J. Nutrition **26**:319 (Sept.) 1943.

Clarified and unclarified honey were assayed for thiamine, riboflavin, pantothenic acid, nicotinic acid and ascorbic acid. The clarified samples showed a general decrease in the concentration of vitamins, ranging from 8 to 45 per cent; however, there was no perceptible reduction in the antihemorrhagic activity of the clarified honeys compared with the unclarified controls.

FREDEEN, Kansas City, Mo.

THE B VITAMINS IN HONEY. GEORGE KITZES, H. A. SCHUETTE and C. A. ELVEHJEM, J. Nutrition **26**: 241 (Sept.) 1943.

Honey contains thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, and folic acid, as determined by microchemical and microbiologic methods. A great variation in amounts was noted, perhaps due to differences in the source and number of grains of pollen present. Aged honeys revealed a decrease in the content of panthothenic acid. Pollen and royal jelly are good sources of the vitamin B complex. Royal jelly is rich in biotin and panthothenic acid, which may be significant in the metabolism of the young bee.

FREDEEN, Kansas City, Mo.

SIGNIFICANCE OF PLASMA ASCORBIC ACID LEVELS IN NEBRASKA CHILDREN. JOHN L. GEDGOUD, VIOLET M. WILDER and JOSEPH A. HENSKE, J. Pediat. **23**: 39 (July) 1943.

The level of ascorbic acid in the plasma was determined for 220 unselected Nebraska children of the lowest income group at the time of admission to the hospital. The results were classified as high (0.7 mg. per hundred cubic centimeters or more), intermediate or borderline (0.4 to 0.69 mg. per hundred cubic centimeters) and low (0.2 to 0.39 mg. per hundred cubic

centimeters). Of the children with high and intermediate levels, one third had infections. However, infection was present in two thirds of the group with low levels of ascorbic acid; the majority of these children were under 2 years of age.

"On a daily intake of 60 to 80 mg. of ascorbic acid, a level of 0.7 mg. per cent or more was attained in 81 per cent of children without infection, regardless of the entrance value.

"The ease of attaining a value of 0.7 mg. per cent or more indicated that 36.4 per cent of 'healthy' children were probably on a diet containing less than from 60 to 80 mg. daily and that levels of from 0.4 to 0.69 mg. per cent may still be considered 'borderline' for that group.

"In two healthy infants entering with plasma levels in the borderline (0.4 to 0.69 mg. per cent) zone, 60 to 80 mg. of ascorbic acid daily did not raise the level beyond 0.7 mg. per cent over observation periods of from eighteen to nineteen days. This is an incidence of two in ninety-six cases (or 2 per cent).

"Of twelve children with infections, acute and chronic, from 100 to 150 mg. ascorbic acid daily was adequate to raise the plasma level to 0.7 mg. per cent or more in eleven, over periods of from three to twenty-one days.

"Only one 'healthy' child persisted in maintaining a low level of plasma ascorbic acid on an intake of from 60 to 80 mg. daily during eleven days of observation."

SHMIGELSKY, Chicago.

INFANTILE SCURVY. DANIEL BLITZ, J. Pediat. **23**:87 (July) 1943.

"The characteristic findings in the roentgenogram taken years after clinical cure are oval, definitely circumscribed areas of rarefaction found in the interior of the epiphyseal centers of ossification. These lesions are always bilateral. These centers of ossification are present in the acute stage of the illness.

"According to Steinberg and Sussman, the blood supply to these centers of ossification is not very rich and is independent of the blood supply to the diaphysis. Upon union of epiphysis with diaphysis there is a concomitant enrichment in the blood supply to the epiphyseal center of ossification and the rarefied area disappears. These investigators feel that these lesions are pathognomonic of healed pre-existent scurvy and may be confused with bone cysts. Schwartz stated that this roentgenologic sign was seen in no other condition. On the other hand, McLean and McIntosh found similar roentgenograms in two cases; one in a patient with acute lymphatic leucemia, another in a patient with anemia of the von Jaksch type. Similar roentgenograms have been found in several cases of healed rickets. These lesions in the epiphyseal centers of ossification may not be pathognomonic of healed pre-existent scurvy, but they are very characteristic of it.

"A case report is presented with the classical symptoms and typical roentgenograms of acute infantile scurvy. A follow-up roentgenogram four and one-half years after clinical cure is presented with the characteristic findings."

AUTHOR'S SUMMARY.

THE EFFECT OF SODIUM DIPHENYL HYDANTOINATE (DILANTIN SODIUM) ON THE UTILIZATION OF ASCORBIC ACID BY GUINEA PIGS. A. D. EMMETT, EVA R. HARTZLER and R. A. BROWN, J. Pharmacol. & Exper. Therap. **78**:215 (July) 1943.

It is well known that the use of diphenylhydantoin sodium in treatment of epilepsy may be accompanied by reactions in the gingiva somewhat simulating scurvy. Experimental evidence hitherto had both supported and denied the claim that the results were due to lowering of the level of vitamin C in the blood. The authors' conclusions are as follows:

"The results indicate: (a) that the dilantin sodium had little or no effect on the gain or loss in weight; (b) that the dilantin sodium treated guinea pigs were able to breed and rear their young; (c) that dilantin did not raise or lower the plasma ascorbic acid levels; (d) that the drug had no influence on the ascorbic acid content of the adrenals, brain, testes and liver; and (e) that there were no gross pathological manifestations of scurvy including gingivitis."

PILCHER, Cleveland.

THIAMIN CHLORIDE—AN AID IN THE SOLUTION OF THE MOSQUITO PROBLEM. W. RAY SHANNON, Minnesota Med. **26**:799 (Sept.) 1943.

Ten cases are reported which appear to be fairly convincing in demonstrating that thiamine hydrochloride in sufficient amounts, if given by either mouth or by injection, is capable of reducing the reactions to mosquito bites. According to the author it causes a rapid recession of welts even of long standing and contributes much to the elimination of the nuisance problem which the mosquito presents. Whether or not it can contribute toward the solution of the health problem depends on many undetermined factors.

STOESSER, Minneapolis.

THE ANTI-THIAMINE FACTOR IN FISH. PHILIP S. OWEN and JOSEPH W. FERREBEE, New England J. Med. **229**:435 (Sept. 9) 1943.

Epidemics of a severe and an unusually fatal paralytic disturbance have been observed in animals when fish has been added to their diet.

The disease is evidently one of thiamine deficiency since it may be produced by thiamine deficiency under experimental conditions and may be cured by injections of thiamine.

There are a number of reasons why thiamine deficiency of this particular origin may not be frequent in man. The portions of fish that are rich in the anti-thiamine factor are for the most part those usually discarded in the preparation of fish for human consumption, that is, viscera, heads, skins and scales. Moreover, the destructive reaction with thiamine is definitely extrinsic since the factor itself is destroyed by peptic digestion by cooking or by drying.

GENGENBACH, Denver.

THE ASCORBIC ACID CONTENT OF LATE-WINTER TOMATOES. ARTHUR D. HOLMES, CARLETON P. JONES and WALTER S. RITCHIE, New England J. Med. **229**:461 (Sept. 16) 1943.

The tomato is generally considered one of the most important of the protective foods, owing largely to its vitamin content. It is commonly classed as a vitamin C food and is frequently listed as one of the richest natural sources of ascorbic acid (vitamin C). Since it can be raised easily even by amateur gardeners, it is almost universally recommended for the home garden.

It is quite evident from the results of this study that the homemaker, the nutritionist and the physician must not consider late winter tomatoes as equivalent to vine matured, sun-ripened summer tomatoes as a source of ascorbic acid for the human dietary. In computing the vitamin C value of late winter tomatoes, one should not assign to them more than one-third the value ordinarily attributed to fully ripe summer tomatoes.

GENGENBACH, Denver.

ACTION OF NICOTINIC ACID ON CARBOHYDRATE METABOLISM. F. J. NEUWAHL, Lancet **2**:348 (Sept. 18) 1943.

Observations were made on the action of nicotinic acid on carbohydrate metabolism in 15 nondiabetic and 12 diabetic subjects.

The depression of the blood sugar curve and the effect of nicotinic acid on the difference in the dextrose content of arterial and venous blood and on the response to injected insulin suggested that nicotinic acid may potentiate the action of insulin.

The administration of nicotinamide to diabetic persons improved the carbohydrate tolerance in every instance. LANGMANN, New York.

## Hygiene; Growth and Nutrition; Public Health

STANDARDS FOR THE BASAL METABOLISM OF CHILDREN FROM 2 TO 15 YEARS OF AGE, INCLUSIVE. ROBERT C. LEWIS, ANNA MARIE DUVAL and ALBERTA ILIFF, J. Pediat. **23**:1 (July) 1943.

Standards for the basal metabolism of children from 2 to 15 years of age, inclusive, have been established on the basis of 1,007 determinations on 70 normal, healthy boys and 718 determinations on 57 normal, healthy girls. In the age range from 2 to 12 years inclusive, the values reported represent the combined results of two consecutive studies of approximately five years each that were found to check each other closely. Further work is now being done to test the validity of the standards for older children.

The bases selected for the establishment of standards are calories per hour per square meter referred to age and calories per hour referred to surface area, weight and height, respectively. The first three methods were chosen because of the relatively low degree of dispersion exhibited, while the last was included because of its wide use.

The results of this study are compared with those of representative reports in the literature, and the role of relative body size in the choice of methods of reference for basal metabolism is included in the discussion.

SHMIGELSKY, Chicago.

MATERNAL AND CHILD HEALTH. JAMES YOUNG, Edinburgh M. J. **50**:474 (Aug.) 1943.

Young emphasizes the fact that the interests of the mother and of the child are unified, forming a state of welfare which is linked by social, economic, nutritional and industrial influences with the health of the community. He discusses community health in relation to the medical schools, the university, the maternity hospital, antenatal and child welfare clinics, social service and continuity of health supervision. However, the most important subject is that of nutrition, since it is concerned with the physical and, as some believe, the mental welfare of the child. A short summary embodies the author's suggestions for bringing about the desired results. NEFF, Kansas City, Mo.

CONTRIBUTION TO THE STUDY OF INFANTILE MORTALITY IN THE CITY OF BUENOS AIRES. F. UGARTE, Rev. Soc. puericult. Buenos Aires **9**:250 (July-Sept.) 1943.

The author presents a statistical picture of the mortality of children under 2 years of age, pointing to intestinal disturbances as the most important cause of death. In recent years the mortality of infants under 30 days old has been diminished considerably, but for children from this age to 2 years it has been decreased only slightly. In the second age group a close relationship between the fluctuations in the number of deaths caused by intestinal disturbances and the seasonal variations in temperature was found; the mortality is greater as the temperature becomes higher and diminishes considerably during the winter. A suggestion is made that the death certificates of infants under 2 years of age contain an account of the feeding employed and a short history of previous illnesses.

In Argentina, as in other countries, more male than female infants are born, and among children under 2 years of age the mortality for male infants is greater than that for female infants. BRIBIESCA, Mexico.

TEACHING OF INFANT CARE IN GRAMMAR SCHOOL. I. PUIG, Rev. Soc. puericult., Buenos Aires **9**:268 (July-Sept.) 1943.

The author proposes that the care of infants should be taught at the end of the grammar school period because girls first have the maternal instinct at this age. Classes could be held in schools, and visits could be made to nurseries. BRIBIESCA, Mexico.

## Prematurity and Congenital Deformities

INTRAUTERINE TRAUMATIC LESIONS OF THE HEART: REPORT OF A CASE, WITH AUTOPSY. W. M. SILVERNAGEL and R. S. FIDLER, Am. Heart J. **26**:129 (July) 1943.

The authors report a case of intrauterine cardiac injury resulting from a nonpenetrating blow to the maternal abdomen. The blow resulted in death of the fetus. The autopsy revealed hemorrhage into the epicardium along the coronary vessels and into the pericardium and pleura, together with hemopericardium and hemothorax. GIBSON, Chicago.

STUDIES IN THE METABOLISM OF THE HUMAN PLACENTA; I. OXYGEN CONSUMPTION IN RELATION TO AGEING. H. W. WANG and L. M. HELLMAN, Bull. Johns Hopkins Hosp. **73**:31 (July) 1943.

The authors point out that the effect of aging of the human placenta on the child and on the mother is unknown and that no metabolic studies have been carried out on human placentas.

The oxygen consumption of the human placenta decreases gradually as pregnancy advances, and this corresponds with the histologic changes in the villi of the organ. The use of analgesics or anesthetics during labor does not influence oxygen consumption.

LYTTLE, New York.

GAIN IN WEIGHT DURING PREGNANCY. HELEN R. ROBINSON, ALAN F. GUTTMACHER, EDMUND P. H. HARRISON JR. and JOHN M. SPENCE JR., Child Development **14**:131 (Sept.) 1943.

In a study of 484 private patients, conducted by three physicians, the gain in weight during the period of gestation was studied and careful records were kept. The economic status of the patients was uniformly good, the women were somewhat older than the average for child-bearing women, and a rather disproportionate percentage (62 per cent) were primigravidas. As a result of the final analysis of the data (restricted to the 299 cases under longest observation) a number of significant conclusions were drawn. Among the more important observations are the following: (1) Cumulative gain in weight over the period of gestation, if

plotted, could almost be characterized as a straight line. Increase was least in the first two months and greatest in the seventh. The total average gain was 24.4 pounds. (2) There was no significant difference between the gain of the primigravidas and that of the multigravidas. (3) The gain in weight during pregnancy was inversely related to the usual weight of the mother. Regulation of diet according to the build of the patient was successful in controlling the gain. (4) Six weeks after delivery, the majority of the women had not yet returned to their prepregnant weight. (5) The greater the total gain during pregnancy, the greater the difference between the postpartum weight and that at the third month of gestation.

A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: III. Demonstration of the Irreversible Conversion of Phenylalanine to Tyrosine in the Human Organism. S. Z. Levine, Margaret Dann and Eleanor Marples, J. Clin. Investigation **22**:551 (July) 1943.

Ten healthy infant boys on constant high protein, vitamin C–free diets were given various doses of levotyrosine and dextrolevophenylalanine in pure form, and the excretion of these aromatic amino acids and their derivatives in the urine was studied. In both premature and full term infants the repeated ingestion of dextrolevophenylalanine resulted in the appearance in the urine not only of this amino acid but of levotyrosine and its derivatives parahydroxyphenylpyruvic acid and parahydroxyphenyllactic acid in large amounts. The reaction is apparently irreversible as shown by the absence of significant excretion of phenylalanine and phenylpyruvic acid after ingestion of equivalent amounts of levotyrosine. Such data suggest that levotyrosine in the diet cannot replace dextrolevophenylalanine, which in animals has been shown to be essential.

Vitamin C, previously shown to diminish or abolish the excretion of aromatic metabolites after single smaller doses, was apparently ineffective when jointly given with repeated larger doses of either tyrosine or phenylalanine.

Guest, Cincinnati.

Spina Bifida and Cranium Bifidum: I. A Survey of Five Hundred and Forty-Six Cases. Franc D. Ingraham and Henry Swan, New England J. Med. **228**:559 (May 6) 1943.

During the last two decades 546 infants and children with spina bifida or cranium bifidum have been seen at the Children's Hospital in Boston.

Race, sex and economic status seem to have little bearing on the incidence of spina bifida.

In 16 (6 per cent) of the 277 cases in which information was available, the patients said there had been spina bifida in the family. Approximately an equal number reported anomalies other than spina bifida in the family.

In 232 patients, or slightly more than half the series, 570 associated anomalies were recorded. Even this large number is probably an underestimate.

A series of 462 cases of spina bifida and 84 of cranium bifidum (encephalocele) is presented, with data on the incidence, sex, race, type, site, associated anomalies and clinical manifestations.

Therapeutic indications and end results are tabulated and discussed.

The age of choice for operations on infants is between 12 and 18 months. This allows time for the development and recognition of disabilities and hydrocephalu for the local growth of skin adequate to permit closur and for the sufficient development of the child stature and nutrition to present a better operative ris

Other factors and conditions are discussed as indica tions for or against operation. Operative procedure are described in detail.

Thirty per cent of the patients with spina bifida a 34 per cent of those with encephalocele may expect relatively normal life. An unduly pessimistic prognos is therefore unwarranted until individual evaluation ha been carefully made.

Gengenbach, Denver.

Spina Bifida and Cranium Bifidum: II. Surgica Treatment. Franc D. Ingraham and Hannib Hamlin, New England J. Med. **228**:631 (May 20 1943.

This well illustrated paper shows the typical co ditions before and after operative treatment of spi bifida and cranium bifidum. Preoperative, operati and postoperative technics are illustrated and discusse in detail.

The essential features of satisfactory treatment o congenital cranial and spinal protrusions are selectio of patients suitable for operation, simple removal a repair of the defect by a technic adapted to the locatio size and shape of the protrusion and meticulous pos operative care. It should be emphasized that a definit hopeless prognosis should rarely be given at the firs examination.

Gengenbach, Denver.

Spina Bifida and Cranium Bifidum: III. Occul Spinal Disorders. Franc D. Ingraham an John J. Lowrey, New England J. Med. **228**:74 (June 10) 1943.

According to the authors, roughly 25 per cent o normal children have occult defects in the vertebra laminas, and the incomplete closure is frequentl demonstrated in roentgenograms taken for some othe reason. The defect is likeliest to occur in the lumba or sacral region and can be shown to have persisted i many normal adults.

The paper is well illustrated. The authors' summar follows:

"An analysis of 65 cases of spina bifida occulta i presented. The symptoms and usual findings a listed.

"Twenty-one cases in which laminectomy was per formed are discussed, and the operative findings sum marized.

"The indications for operation were specific, an operation was not performed without a definite histor of progressive difficulty.

"In only 2 out of the 21 cases did operation fail t show a lesion that might account for the presentin complaint. In the large majority operation showed definite lesion affecting the cauda equina or nerv roots, that could be remedied surgically.

"The findings suggest that probably more of th questionable cases should be offered the benefit o exploration."

Gengenbach, Denver.

The Significance of Fetal Hiccups. W. A. McGe South. M. J. **36**:508 (July) 1943.

The author states the belief that fetal hiccups a definitely related to allergic states in the infant and th the attending physician should keep this in mind planning any initial feeding regimen.

Schlutz, Chicago.

ONGENITAL DEFECTS IN INFANTS FOLLOWING INFECTIOUS DISEASES DURING PREGNANCY. C. SWAN, A. L. TOSTEVIN, B. MOORE, H. MAYO and G. H. BLACK, M. J. Australia **2**:201 (Sept. 11) 1943.

As a result of a questionnaire sent to all medical practitioners in southern Australia the authors were enabled to study the relationship between acute exanthems during pregnancy and congenital defects in infants in 61 cases. Of the 61 infants, 36 had congenital defects. Forty-nine of the mothers had had rubella, 9 had contracted morbilli and 2 had had mumps during the period of pregnancy. Four mothers had no knowledge of any exanthem occurring during this time. Of the 49 infants born to mothers who had rubella during pregnancy 31 exhibited congenital defects. The abnormalities included cataract (in 13 infants of whom 7 had other defects), deaf-mutism (in 7 infants, 2 of whom had associated defects), heart disease (in 17 infants, 11 of whom had associated defects), microcephaly (in 3 infants), hypospadias (in 1 infant), clubfoot (in 1 infant), mongolism (in 1 infant) and mental retardation. With 2 exceptions all of the 31 mothers with congenitally defective children had contracted rubella within the first three months of pregnancy. The mothers of 4 of the infants with congenital cataract, associated with other defects in 3 instances, denied all knowledge of an exanthem during pregnancy.

No congenitally defective babies were born to mothers who had morbilli in pregnancy. One mother who had mumps during pregnancy gave birth to a child with a congenital corneal opacity.

GONCE, Madison, Wis.

EDICOSOCIAL PROBLEM OF PREMATURE INFANTS. JUAN J. MURTAGH, Rev. Soc. puericult. Buenos Aires **9**:229 (July-Sept) 1943.

The author reviews the etiologic factors in prematurity; he ascribes 10 per cent of the premature births in Buenos Aires to syphilis.

He urges that obstetricians try to diminish as much as possible the common causes of prematurity, to give to the premature infant the right care, and to cooperate with the pediatrician. The latter should care for the infant, with the aid of special nurses and of complete equipment, consisting of ambulances, incubators, oxygen tents and warm cribs. He also suggests that social workers give special advice to future mothers.

BRIBIESCA, Mexico.

## Newborn

NEUMOTHORAX IN THE NEWBORN INFANT. G. W. SALMON and G. B. FORBES, J. Pediat. **23**:50 (July) 1943.

Pneumothorax is not infrequent in the neonatal period and may be associated with alarming signs of respiratory difficulty. Two possible causes to be considered are (1) the presence of a pathologic condition in the respiratory tract and (2) overdistention of the alveoli. Either or both of these may weaken the walls of the respiratory tract and lead to a break in their continuity resulting in the appearance of air outside the normal pathways. Pneumothorax secondary to the first cause probably arises by a direct rupture of the visceral pleura, while pneumothorax due to the second cause is more likely to follow the mechanism described by Macklin; air travels from the pulmonary interstitial tissue to the mediastinum producing mediastinal emphysema and then ruptures the mediastinal pleura to produce pneumothorax. In this second type the pneumothorax is more likely to be the result of the respiratory difficulty than the cause.

SHMIGELSKY, Chicago.

BRONCHOSCOPY IN THE NEWBORN INFANT. FLETCHER D. WOODWARD and WILLIAM W. WADDELL JR., J. Pediat. **23**:79 (July) 1943.

When indicated bronchoscopy is a life-saving procedure. Woodward and Waddell present reports to illustrate the safety and value of bronchoscopy in the newborn infant. At present the indications for bronchoscopy in the newborn infant are not clearcut, and it is done only when the usual procedures have failed. The authors advise that bronchoscopy be used more frequently in all types of congenital atelectasis.

In 1 case described, a 5½ pound (2,495 Gm.) twin was hospitalized six hours after birth because of persistant cyanosis and dyspnea which cleared with administration of oxygen but returned when the baby was taken out of the incubator. A roentgenogram of the chest revealed collapse of the left lung with the heart and mediastinum drawn to the left. Since no improvement occurred in three days, a 3.5 mm. bronchoscope was introduced and suction was applied to the left bronchus. The procedure lasted three minutes. Prompt improvement followed and a roentgenogram taken two days later showed normal aeration.

The second case reported was that of a newborn premature infant (1,860 Gm.) with massive congenital atelectasis of the left lung due to absence of the left main bronchus. The baby was examined bronchoscopically at 9 days of age with a 3.5 mm. bronchoscope and again at 18 days of age. When the infant was 26 days old, 2 cc. of iodized poppyseed oil was injected into the trachea through a laryngoscope; roentgenograms were taken, and the oil was removed by suction. The procedure was well tolerated. The child is now 16 months old, and the left lung is still unaerated.

A case of massive congenital atelectasis of the left lung due to congenital absence of the left main bronchus in an 11 year old boy is presented because of its rarity and interest.

Cases of partial congenital atelectasis and pneumothorax in 2 newborn infants who died several hours after bronchoscopy are described. Autopsies were not permitted. In these 2 cases the procedure was well tolerated, and death was not deemed due to bronchoscopy.

SHMIGELSKY, Chicago.

TWO CASES ILLUSTRATING THE TREATMENT OF NEONATAL PNEUMONIA. R. A. RATCLIFF, Arch. Dis. Childhood **17**:153 (Sept) 1942.

Two cases of neonatal pneumonia, associated with aspiration of contents of the amniotic sac and subsequent recovery, are described. The treatment is discussed with particular reference to the rapid improvement which followed injection of human serum.

KELLY, Milwaukee.

MODERN VIEWS OF JAUNDICE IN THE NEWBORN. REGINALD LIGHTWOOD, Practitioner **150**:286 (May) 1943.

The author presents interesting classifications and an excellent review of fetal erythroblastosis. Of special interest are some of the references to early speculation in regard to the antigen-antibody reaction and the possibility of disease states due to it in human beings.

THELANDER, San Francisco.

## Acute Infectious Diseases

STUDIES ON THE EFFECTIVENESS OF PHENOTHIAZINE IN HUMAN NEMATODE INFECTIONS. HARRY MOST, Am. J. Trop. Med. **23**:459 (July) 1943.

The authors experimented with phenothiazine in patients with various nematode infections. They concluded that it was effective in the treatment of human Enterobius vermicularis infections. A total dose of 300 mg. per kilogram of body weight administered during three days is recommended pending further investigation, as it is toxic in large doses, causing hemolytic anemia and hepatitis. It was found ineffective against infections with Ascaris lumbricoides, Necator Americanus, Strongyloides stercoralis and Trichocephalus trichiurus.

BURPEE, Augusta, Ga.

CHRONIC TOXOPLASMOSIS. DAVID WEINMAN, J. Infect. Dis. **73**:85 (July-Aug.) 1943.

This relatively new type of infection needs no better introduction than a perusal of the author's summary, which follows:

"Immunity in murine toxoplasma infections was relative only. It resulted in recovery from the acute attack, and for a time protected against reinoculation, but did not result in elimination of the organism.

"Mice which recovered from an acute attack became chronic carriers; in some the infection was inapparent for a time, others died long after inoculation; organisms recovered from all carriers were virulent for other animals.

"The brain of the carriers was the organ most heavily and most regularly infected following any route of inoculation.

"The pathological findings in the chronic toxoplasmosis of healthy carrier mice were quite at variance with those observed in the acute disease; notably the inflammatory necrotic lesions were uncommon despite abundance of virulent organisms.

"Toxoplasmas persisted in the pseudocyst form in carrier mice. The pseudocysts provoked less tissue damage and appeared to be more resistant than single isolated parasites.

"Human chronic toxoplasmosis has not yet been demonstrated. The close correspondence between the disease in man and in animals, and the existence of healthy human parents who transmit the infection to their offspring, make it very nearly certain that chronic infections exist in man also." TOOMEY, Cleveland.

BASAL METABOLISM IN RHEUMATIC CHILDREN. EDWARD E. BROWN and VALENTINA P. WASSON, J. Pediat. **23**:19 (July) 1943.

Basal metabolic rates were determined by the Benedict method for 97 boys and girls with rheumatic fever, from 8 to 17 years of age. The basal metabolic rates were low in most of these children, and reached the lowest level in the spring. The rates averaged —7.6 per cent. Continuous colds during the winter and spring months are considered an important factor. The primary infection is believed to be a chronic suppurative sinusitis, and despite the removal of tonsils and adenoids the majority of the children had adenitis of the cervical, submaxillary or retropharyngeal glands in the spring when the sinusitis and rheumatic activity were at their height.

The toxins causing the adenitis "are probably responsible for damage to the thyroid gland with consequent lowering of the basal metabolic rates."

SHMIGELSKY, Chicago.

IMMUNIZATION AGAINST RHEUMATIC FEVER. VALENTINA P. WASSON and EDWARD E. BROWN, J. Pediat. **23**:24 (July) 1943.

To prevent recurrences of rheumatic fever, 80 children in the ambulatory stage of rheumatic cardiac disease were given intradermal inoculations of tannic acid–precipitated toxin of the N. Y. 5 strain of hemolytic streptococci. Five inoculations were given each patient during the first winter of treatment and two a year thereafter. No general reaction or abscess formation occurred. All the patients reported some itching at the site of injections and usually some local tenderness, swelling and redness.

The results of this "short method" of immunization compare well with those of the "long method," requiring at least thirty-eight subcutaneous injections of crude toxin given over a period of two years. The children benefited by this prophylactic treatment and suffered no relapses. SHMIGELSKY, Chicago.

THE SANATORIUM METHOD FOR THE CARE OF RHEUMATIC HEART DISEASE IN CHILDREN. LEO M. TARAN, J. Pediat. **23**:69 (July) 1943.

A sanatorium for the treatment of children suffering from acute rheumatic disease is described in detail. The institution consists of six small units each accommodating 25 children. Children 6 to 15 years of age are accepted during the active phase of the illness and treated at the sanatorium for a period of at least six months after subsidence of clinical evidence of active rheumatic disease. Definite criteria are followed in deciding the duration of the stay, but each case is judged on its own merits.

The sanatorium is fully equipped to deal with any cardiac emergency and with all types of acute rheumatic manifestations. The clinical course and results of complete laboratory tests are recorded in full detail on forms devised for a threefold purpose: (1) to obtain an accurate history of the course of the active rheumatic disease; (2) to detect early signs of recurrent activity, and (3) to establish criteria for rheumatic quiescence.

Therapy is based on the principle that rheumatic disease is protracted, of months' duration. A careful psychologic approach to the patient is considered of great importance. An attempt is made to adjust the professional care to the individuality of each child. An atmosphere of encouragement and hope for rapid and complete recovery is created by the carefree and undisciplined manner of the medical personnel.

Bedside teaching of the children as well as occupational therapy is continued during the acute phase. The transition from activities and routines of the acute to those of the subacute and finally to those of the quiescent phase is watched carefully and conducted slowly. Finally an attempt is made to bring about an easy transition from the sanatorium to home care.

The sanatorium has a varied medical educational program. The physiologic and pathologic aspects of heart disease are studied clinically and in the laboratories. Active research is conducted along three main lines: clinical cardiology; cardiac physiology, and bacteriology and immunology.

The St. Francis Sanatorium for Cardiac Children has been established on the principle that rheumatic disease in children, in the acute stage, cannot be adequately treated under the conditions present in the usual children's hospital. The medical policies governing this institution evolved from the concepts that (1) the active phase of rheumatic disease in children is of much longer duration than the clinical signs would see

o show; (*b*) the usual clinical and laboratory diagnostic riteria are inadequate in a great many cases of acute heumatic infection; (*c*) the so-called subclinical phase f acute rheumatic disease deserves as much thera- eutic consideration as the well known acute rheumatic rthritis or carditis, and (*d*) the function of the sana- orium is to attempt to prevent further cardiac damage y active treatment of acute and subacute rheumatic nfection. Five years' experience at the sanatorium ives definite encouragement for continuance of the olicy as formulated.

SHMIGELSKY, Chicago.

MMUNIZATION IN PEDIATRICS. C. J. BLOOM, South. M. J. **36**:495 (July) 1943.

The author presents a good review of the origin of mmunizing agents and gives an illuminating evaluation f them, showing many successes and relatively few ailures. He points out that the incidences of the dis- ases for which the patients were immunized and the espective death rates have been notably reduced by he systematic use of these agents in children.

SCHLUTZ, Chicago.

THE ETIOLOGY OF RHEUMATISM. WALTER M. LEVINTHAL, Edinburgh M. J. **50**:415 (July) 1943.

The author is bacteriologist in the Royal College of Physician's Laboratory at Edinburgh. He reviews here he fact that the lesion of rheumatism begins locally nd in the mesodermal tissues of the body; that it is lways the connective tissue which is the point of ttack in the involved organ, whether the manifest esion is arthritis, fibrosis or neuritis, and that the isease is systemic in spite of the local areas involved. The morphologic pattern of the rheumatic damage to issue began to be studied with the discovery of the schoff nodule. The knowledge of the pathology has rown much in the last two generations, and there is ow much evidence that there is a close connection etween infection and rheumatic disease. However, heumatic symptoms may be a feature of many infectious iseases, a fact which suggests that rheumatism is an naphylactic condition. Levinthal discusses the mecha- ism of anaphylaxis and concludes in his summary hat both acute and chronic rheumatism are evidences f such a state, in which multiple lesions in the meso- ermal system are brought about by continual antigen- ntibody reactions on tissue cells.

The author is to supplement this article with a survey, n a later edition of the same journal, of the therapeutic ossibilities in rheumatic disease.

NEFF, Kansas City, Mo.

## Diseases of Blood, Heart and Blood Vessels and Spleen

FRACTIONATION OF THE SERUM AND PLASMA PROTEINS BY SALT PRECIPITATION IN INFANTS AND CHILDREN: I. THE CHANGES WITH MATURITY AND AGE; II. THE CHANGES IN GLOMERULONEPHRITIS; III. THE CHANGES IN NEPHROSIS. MILTON RAPOPORT, MITCHELL I. RUBIN and DORCAS CHAFFEE, J. Clin. Investigation **22**:487 (July) 1943.

In premature and full term newborn infants, older nfants and young children the levels of blood fibrin were found to be constant at all ages and equal to adult values; the level of total serum protein was found o rise with increasing maturity, with both albumin and globulin fractions involved in the incerase but with a proportionately greater increase in the globulin fraction. Throughout infancy certain of the globulin fractions (probably gamma globulin) were present in lower concentrations than those found in young children.

In children with glomerulonephritis the plasma fibrin was elevated during the acute stage of the disease and returned to normal with healing; but it remained persistently elevated in the chronic phase of the disease. In acute glomerulonephritis the serum albumin was slightly lowered, but in the chronic stages both serum albumin and globulin were reduced. In acute glomerulonephritis a globulin subfraction (gamma globulin) increased, and returned to its normal level with healing, but it was reduced in value in chronic nephritis.

During the active phase of lipid nephrosis the level of the plasma fibrin was elevated while the well known reductions in total serum protein and albumin and normal or slightly elevated concentrations of serum globulin were encountered. The globulin fraction presumed to be gamma globulin was reduced during the active phase of the disease but returned to a normal value with subsidence of the acute edematous stage.

GUEST, Cincinnati.

THE ROLE OF DIETARY PROTEIN IN HEMOGLOBIN FORMATION. ALINE UNDERHILL ORTEN and JAMES M. ORTEN, J. Nutrition **26**:21 (July) 1943.

An adequate dietary intake of protein is essential for the normal formation of hemoglobin in the rat.

FREDEEN, Kansas City, Mo.

SEVERE SUBLINGUAL AND PARATRACHEAL HEMORRHAGE IN HEMOPHILIA WITH RECOVERY FOLLOWING TRACHEOTOMY. KATHERINE H. BAIRD and MEYER S. FOX, J. Pediat. **23**:90 (July) 1943.

One type of hemorrhage in hemophilia is of especial danger, that is, bleeding into the sublingual and paratracheal tissue which may produce asphyxia before the loss of blood is in itself significant.

A review of the literature reveals reports of 7 cases of such bleeding. In 4 cases the symptoms were not sufficient to warrant tracheotomy and the patients lived. In 3 cases in which tracheotomy was necessary the patients died.

The case reported is that of a 4½ year old hemophilic boy in whom a massive sublingual and paratracheal hemorrhage developed during the course of an infection of the upper portion of the respiratory system. Tracheotomy became necessary and was successfully performed, with immediate relief of the respiratory distress. Favorable progress followed the use of repeated large transfusions of blood totaling 2,850 cc.

SHMIGELSKY, Chicago.

## Diseases of Nose, Throat and Ear

THE TREATMENT OF TONSILLITIS, PHARYNGITIS AND GINGIVOSTOMATITIS WITH THE BISMUTH SALT OF HEPTADIENECARBOXYLIC ACID IN COCOA BUTTER SUPPOSITORIES. SAMUEL SILBER, J. Pediat. **23**:59 (July) 1943.

Since the inauguration of the successful use of salts of bismuth in the treatment of infections of the buccal cavity by Monteiro during the past two decades, corroboration of his observations has come from many quarters. The use of various salts of bismuth, such as the subsalicylate, the subgallate and sodium iodobismuthate, in doses of 0.05 Gm. of bismuth, injected at twenty-four to forty-eight hour intervals, produced a drop in temperature within twelve to twenty-four hours, and within forty-eight to seventy-two hours recession

of symptoms and signs, including exudate, swelling, tenderness, pain and dysphagia. Marinho, Rastelli, Mangabeira-Albernaz, Stiehr, Koehler, Boese, Imhof, Vaz de Mello, Galewski and others found repeatedly that this method was effective in cases of tonsillitis, and that gingivostomatitis (Vincent's) responded more rapidly to it than to any other form of treatment. The effectiveness of bismuth compounds in the treatment of patients harboring streptococci was shown by Monteiro and by Ricquet. Lewis, however, stressed the fuso-spirochetal nature of tonsillar infections in reporting the rapid response of his patients, within twenty-four to forty-eight hours, to "specific treatment" with compounds of arsenic or preferably of bismuth. He expressed the hope, however, that treatment by injection might be avoided.

Silber reports the use of the bismuth salt of hepta-dienecarboxylic acid in cocoa butter suppositories as the ideal treatment for tonsillitis, pharyngitis and gingivostomatitis. In the size for infants the suppositories contain 0.0675 Gm. of the bismuth salt, equivalent to 0.0225 Gm. of metallic bismuth, and the dose for adults is double that for infants. He cites the use of such suppositories by Kowarz, by Alpar and Weisz and by Orso with results identical with those obtained by him.

In 32 cases of infections in children, Silber reports the disappearance of symptoms within twenty-four to forty-eight hours after the beginning of treatment, defervescence beginning in twenty-four hours and being practically complete in forty-eight hours. Subjective symptoms began to disappear and there was local improvement in twenty-four hours. Exudate, swelling, pain and dysphagia disappeared as rapidly in cases in which suppositories were used as in those in which injections were given. However, by dispensing with painful injections, by avoiding the inflamed tissues of the throat, by requiring at most two treatments twenty-four hours apart, these suppositories stand out as ideal for use in children. Silber concludes that the treatment he describes for tonsillitis, pharyngitis and gingivostomatitis is to be preferred to all others, including the use of sulfonamide drugs, because (1) it is of equal or greater therapeutic value; (2) it has the advantage of ease of administration, and (3) its use reserves the sulfonamide drugs for conditions in which they are definitely indicated or specifically required and thus avoids production of sensitivity to sulfonamide compounds. The absence of local ill effects or of systemic toxic effects of bismuth increases the desirability of this choice by the additional factor of greater safety.

SHMIGELSKY, Chicago.

ACUTE LARYNGOTRACHEOBRONCHITIS IN CHILDREN. JOHN A. V. DAVIES, New England J. Med. **229**:197 (July 29) 1943.

In past years acute laryngotracheobronchitis has carried a mortality of 50 to 100 per cent.

It must be differentiated from simple spasmodic croup and laryngeal diphtheria, usually by its acute onset and the rapid progress of its symptoms.

Almost 50 per cent of the patients are 2 years of age and under.

There has been a tendency to consider beta hemolytic streptococci as the only organisms involved, whereas Staphylococcus aureus, Haemophilus influenzae and pneumococci are also frequently present.

Treatment may be started with sulfathiazole or sulfadiazine or with penicillin if it is available. Inhalations of cool oxygen appear more helpful than steam. All preparations should be made for tracheotomy should it become necessary, including insuring the availability of an aspirator. The insertion of a Mosher tube into the trachea may prove a life-saving measure.

GENGENBACH, Denver.

THE USE OF SULFONAMIDES IN THE TREATMENT OF RESPIRATORY INFECTIONS IN CHILDREN. CHARLES A. JANEWAY, New England J. Med. **229**:201 (July 29) 1943.

What are the indications for the use of sulfonamide drugs in the treatment of infections of the respiratory tract in children? They boil down to evidence of an acute bacterial infection of the respiratory tract that is obviously spreading and is serious or potentially serious.

What drugs can be used? Sulfadiazine is obviously the most satisfactory of the sulfonamide drugs; it disturbs children as well as adults much less in every way. The sodium salt of sulfadiazine can be given parenterally with great ease, and it therefore is the ideal drug.

Sulfathiazole can be used in the same doses as sulfadiazine, except that one must remember that sulfathiazole is much more rapidly excreted and that it is therefore more difficult to maintain an adequate concentration in the child by parenteral use of the drug without getting renal complications.

The dosage in general, if one goes by rule of thumb, is approximately 1 grain (0.06 Gm.) per pound (0.1 Kg.) for the first twenty-four hours for any serious infection. If a child is seriously ill, one half to three quarters of this amount is given as an initial dose.

These drugs cannot be given satisfactorily by rectum.

GENGENBACH, Denver.

PERILARYNGEAL CYSTS. JUSTO M. ALONSO and ELIAS REGULES, Rev. de otorrinolaring. **3**:15 (June) 1943.

Alonso and Regules present 2 cases of perilaryngeal cysts. These are congenital laryngeal cysts or cystic laryngoceles on the inner and the upper part of the thyroid cartilage and outside of the laryngeal muscles. The principal finding is an elevation of the base of the epiglottis and the ventricular band. Both patients were treated surgically. The cysts were removed by an external incision, and there were no recurrences.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

## Diseases of Lungs, Pleura and Mediastinum

THE WELTMANN REACTION IN BRONCHIAL ASTHMA. SUSAN C. DEES, J. Allergy **14**:469 (Sept.) 1943.

The Weltmann reaction was studied in a series of 224 persons with asthma (51 children and 173 adults).

Patients with uncomplicated asthma or asthma and another allergic disease had coagulation bands of 6, except 6 patients with intrinsic asthma due to bacterial allergy and intrapulmonary infections, who had bands of 5.

Patients with asthma and noninfectious complications had bands of 7 or greater. All patients with infections had bands less than 6, except a group of 24 patients with chronic infection. One half of these had very mild infections. The other half had, in addition to infection, some marked degree of emphysema or pulmonary fibrosis.

On the basis of the Weltmann reaction one may apparently detect the presence of infection and fibrotic change in persons with asthma. HOYER, Cincinnati.

THE USE OF AMINOPHYLLINE RECTAL SUPPOSITORIES IN THE TREATMENT OF BRONCHIAL ASTHMA. SUSAN C. DEES, J. Allergy **14**:492 (Sept.) 1943.

Rectal suppositories containing 0.25 Gm. of aminophylline gave definite relief of symptoms to a group of patients with severe asthma.

The suppositories may be used at bedtime and not oftener than every six hours during the day.

Aminophylline may be administered by other routes or used in combination with other antispasmodics if desired. The suppositories fill the need for a drug that will act over a long period of time and that can be self administered. HOYER, Cincinnati.

CHLORIDE METABOLISM AND PLASMA AMINO ACID LEVELS IN PRIMARY ATYPICAL PNEUMONIA. KENDALL EMERSON JR., EDWARD CHARLES CURNEN, GEORGE SWOPE MIRICK and JAMES EDWIN ZIEGLER JR., J. Clin. Investigation **22**:695 (Sept.) 1943.

In primary atypical pneumonia, unlike pneumococcic pneumonia, hypoaminoacidemia does not occur, and there is no significant tendency to retain salt and water in the acute stage or to excrete an excess of these substances in convalescence. [AUTHORS' SUMMARY.]

THE OCCURRENCE OF SULFONAMIDE-RESISTANT PNEUMOCOCCI IN CLINICAL PRACTICE. MORTON HAMBURGER JR., L. H. SCHMIDT, CLARA L. SESLER, J. M. RUEGSEGGER and EDNA S. GRUPEN, J. Infect. Dis. **73**:12 (July-Aug.) 1943.

The authors point out that pneumococci resistant to sulfonamide compounds occur rarely, if at all, in untreated patients, though pneumococci may acquire resistance during the administration of sulfonamide drugs to patients. When the course of treatment is brief, as in the routine therapy of pneumonia, resistant organisms are not frequently developed. When the treatment must be prolonged, as in the therapy of endocarditis or slowly resolving pneumonia, the development of resistant pneumococci seems to be a regular occurrence.

This may constitute a health hazard in the future, because recovery may take place despite the presence of moderately resistant organisms, and clinical cure brought about by sulfonamide compounds is frequently accompanied by a carrier state lasting weeks, months or even years. TOOMEY, Cleveland.

SUDDEN DEATH IN INFANTS DUE TO PNEUMONIA. JOHN M. ADAMS, J. Pediat. **23**:189 (Aug.) 1943.

Pneumonia is probably the most important single cause of sudden death of infants thought to be essentially well. An interstitial infiltration by mononuclear cells was the most outstanding and constant histologic characteristic of the lung tissue in the cases reported. Additional prominent features were hemorrhage and edema. These changes were similar to those recorded by the author in fatal virus pneumonitis. All patients with the latter disease showed, in addition, proliferation and desquamation of bronchial and bronchiolar epithelium and the presence of cytoplasmic inclusion bodies in these cells. Rivers and Sprunt both state that a mononuclear reaction is characteristic in the acute phase of virus diseases. The absence of bacteria and the almost complete lack of polymorphonuclear leukocytes in the microscopic sections suggested a virus as the agent of infection. Additional evidence in favor of this assumption is afforded by the fact that the marked mononuclear infiltrations demonstrated were similar to those observed in experimentally produced virus pneumonitis. SONTAG, Yellow Springs, Ohio.

MORTALITY IN ACUTE STAPHYLOCOCCAL EMPYEMA IN INFANTS AND CHILDREN. WILLIAM E. LADD and HENRY SWAN, J. Pediat. **23**:297 (Sept.) 1943.

Ladd and Swan reported the results of 33 cases in which patients with staphylococcal empyema were treated at Children's Hospital in Boston.

Empyema due to staphylococci is more rare than that due to pneumococci or to streptococci.

It has usually been believed that the mortality from staphylococcic empyema was far higher than that from empyema due to other organisms. Ladd and Swan pointed out that this was not true in their series except in a limited age group. There appears to be a sharp dividing line at 4 months of age, before which the mortality is extremely high and after which the mortality is low. This prominent effect of age on mortality had not previously been reported. It is also pointed out that the staphylococcic infection was more likely to be accompanied or followed by multiple complications and infections with other organisms but that this did not affect the mortality. This strongly suggested that the pathologic and immunologic response in infants under 4 months of age is quite different from that found in later age groups. In postmortem examinations it was observed that the empyema had been adequately drained and the lung had been either partially or completely reexpanded. The cause of death was in most instances a progression of the underlying staphylococcic pneumonic process associated with generalized infection.

Adequate drainage of the empyema is recommended, and it was suggested that a decrease in mortality in the future would probably result from improved therapy of the streptococcic pneumonia rather than from any change in surgical procedure.

SONTAG, Yellow Springs, Ohio.

CONGENITAL PULMONARY CYSTS. CARL C. FISCHER, FRANK TROPEA JR. and CHARLES P. BAILEY, J. Pediat. **23**:219 (Aug.) 1943.

The authors describe the case of an infant who showed the signs and symptoms of expansile balloon cysts of the upper and middle lobes of the right lung.

As aspiration of the air in the cysts failed to produce any improvement in the infant's condition, lobectomy was performed when the child was 4 weeks of age. The infant recovered uneventfully, with remission of all symptoms and gradual absorption of the air as indicated by the disappearance of the basal shadow revealed by roentgenograms in the area of the extirpated lobes.

A brief discussion of other possible methods of treatment is outlined, the authors concluding with a plea for the more frequent use of lobectomy as the treatment of choice for this type of congenital anomaly in infants. SHMIGELSKY, Chicago.

CYSTIC CONDITIONS IN THE LUNG. C. ELAINE FIELD, Proc. Roy. Soc. Med. **36**:584 (Sept.) 1943.

Intrapulmonary cystic conditions of the lung may be differentiated into those usually considered congenital in origin and those developing after birth. The frequency of other congenital anomalies in association with cystic lungs supports the theory of congenital origin. Three cases of the congenital type in patients aged 5½, 6½ and 3½ years and 1 case of the acquired type in a girl of 11½ years are reported. The treatment of both types is discussed and roentgenograms for 2 cases accompany the report.

WILLIAMSON, New Orleans.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

SUBDIAPHRAGMATIC ABSCESS IN CHILDREN. WILLIAM E. LADD and HENRY SWAN, New England J. Med. **229**:1 (July 1) 1943.

It is generally agreed that the mortality of untreated subdiaphragmatic abscess is between 90 and 100 per cent. Fourteen patients have been seen at the Children's and Infants' Hospitals in whom an abscess in the subdiaphragmatic space has been recognized. Eleven of these were treated surgically, with 1 death; the other 3 died with fulminating infection, and at autopsy a subphrenic abscess was found in each, as one among multiple manifestations of generalized sepsis.

The present series comprises 14 patients under 11 years of age, 6 of whom were less than 2 years old. There were 9 boys and 5 girls. All but 1 of the patients were white. In 5 of the patients (36 per cent) the abscesses were secondary to suppurative appendicitis.

Exact preoperative localization of a subdiaphragmatic abscess is more difficult in children than in adults.

In surgical intervention the extraserous approach is by all odds the one of choice. Such a procedure, with the incision in the midaxillary line just below the costal margin, is advocated for use in children.

GENGENBACH, Denver.

## Psychology and Psychiatry

STUDIES ON THE PROGNOSIS IN SCHIZOPHRENIC-LIKE PSYCHOSES IN CHILDREN. R. S. LOURIE, B. L. PACELLA and Z. A. PIOTROWSKI, Am. J. Psychiat. **99**:542 (Jan.) 1943.

Lourie, Pacella and Piotrowski studied 20 children who at some time before the age of 12 years experienced psychotic episodes classifiable as schizophrenia of childhood. The group comprised 15 boys and 5 girls who presented a psychotic picture characterized by deterioration from a previous level. The average period of hospitalization was ten months. The average follow-up period was eight years. At the end of the periods of observation the following levels of adjustment were observed: An apparently normal adjustment had been made by 4 patients; fair to borderline adjustments, by 5 patients, and low grade adjustments, by the remaining 11 patients. Of the last group, 3 manifested reactions of adult schizophrenia, 5 maintained their level at the time of hospitalization or deteriorated further and in 3 an organic basis was established. In the vegetative sphere, it was striking that all patients who failed to improve remained physically infantile. Anxiety when associated with resignation was of poor prognostic significance. Psychometric data with regard to intellectual and perceptual assets offered prognostic aid. The patients capable of cooperation in the Rohrschach tests showed improvement. Electroencephalographic studies showed no definite correlation with the psychotic picture.

FORSTER, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

STREPHOSYMBOLIA: A PEDIATRIC AND PEDAGOGIC PROBLEM. CHAUNCEY W. WYCKOFF, J. Pediat. **23**:95 (July) 1943.

The term strephosymbolia, meaning mixed symbols, was first used in this capacity by Dr. S. T. Orton, formerly a professor of neurology at Columbia University, in classifying certain children having difficulty in learning to read, children who mixed up the letters or symbols in words or read the word with letters reversed or from right to left. Such children in the past have been erroneously classified as having a developmental defect called congenital word blindness. Orton contends that the basis of the difficulty is mixed cerebral dominance; these children are neither wholly right nor wholly left sided. The fact that a child may fail to learn to read although of adequate intelligence is receiving increasing attention from educators, psychiatrists and pediatricians. There are three highly developed recording mechanisms through which reading may be learned; (1) feeling or kinesthesia, which is highly developed in the blind, (2) the auditory sense and (3) the visual mechanism.

Children with mixed cerebral dominance have great difficulty in visualizing the letters and words, as the images are recorded on both sides of the brain but opposite in sign and the impression on one side must be deleted or made inactive to obtain a correct result or else mirror reading results.

Unfortunately there is no way of ascertaining whether a child is going to have this difficulty in learning to read until he has been subjected to the test of learning for a year or two. Orton claims that 1 to 2 per cent of the school population have a very definite degree of strephosymbolia and that up to 4 per cent have mild gradations but eventually adjust themselves.

Monroe claims that 12 per cent of children of school age have some degree of this difficulty. Unrecognized and untreated, children with a severe degree of strephosymbolia may easily acquire an inferiority complex, emotional unbalance and an asocial attitude which may readily lead to delinquency. There are several tests for the detection of this difficulty. Vision, especially fusion, should be tested; auditory tests should be made if from previous examination one is not positive that the tests of laterality were conclusive.

There are numerous borderline cases in which there is no history of sidedness and results of tests appear to be negative, and yet the child has sufficient difficulty to warrant special teaching. There is only one method of teaching such children to read, that is, by the auditory or phonetic approach, supplemented by the finger or kinesthetic method. Many of the children with severe or moderately severe strephosymbolia should be taken out of school entirely for a year or more and given this special instruction by properly trained tutors.

SHMIGELSKY, Chicago.

DEMENTIA INFANTILIS WITH CORTICAL DYSRHYTHMIA. ALEXANDER KENNEDY and DENIS HILL, Arch. Dis. Childhood **17**:122 (Sept.) 1942.

A case of dementia with catatonic behavior in a 6 year old patient is described, in whom a marked cortical dysrhythmia was found on electroencephalographic examination.

The clinical similarity between this condition and the schizophrenia-like psychoses of childhood is discussed.

No definite relationship was observed between the abnormalities of the electric rhythm and the clinical state of the patient at the time of taking the records.

Abnormal electric records were obtained from both parents.

Long series of repeated electric complexes of petit mal type were recorded. Although these were of uniquely long duration, they were not accompanied by clinical attacks until the frequency of the complexes had risen to three per second.

It is suggested that some of the recorded cases of dementia infantilis may have been cases of epileptic

mentia in which the dysrhythmia was present without ward clinical manifestation. The name dementia rhythmica infantum might be applied to this syndrome.

KELLY, Milwaukee.

## Diseases of the Ductless Glands; Endocrinology

RAPID TEST FOR PREGNANCY GONADOTROPINS ON THE BASIS OF INDUCED OVULATION IN MICE. H. O. BURDICK, HUBER WATSON, VINCENT CIAMPA and THOMAS CIAMPA, Endocrinology **33**:1 (July) 1943.

It is demonstrated that ovulation can be induced in ce within twenty-four hours after a single subcutaous injection of chorionic gonadotropin.

Induced ovulation in the mouse is such a definite end int for a bio-assay that it warrants further investiion as a rapid test of the potency of gonadotropins. appears to be of definite value as an eighteen to enty-four hour test for pregnancy.

JACOBSEN, Buffalo.

HIBITION OF ESTROGENIC EFFECTS ON THE REPRODUCTIVE SYSTEM OF THE MALE RAT BY TESTOSTERONE INJECTIONS. CHARLES K. WEICHERT and HENRY B. HALE, Endocrinology **33**:16 (July) 1943.

It is demonstrated that in rats testosterone prevents thylstilbestrol from exerting its effects. The experints suggest that as the normal animal gets older it es its capacity to respond to estrogenic stimulation ause of the gradual increase in secretion of andron by the intact testes.

JACOBSEN, Buffalo.

NEFICIAL EFFECT OF ESTROGENS ON ALTITUDE TOLERANCE OF RATS. BERNARD D. DAVIS and BENJAMIN F. JONES, Endocrinology **33**:23 (July) 1943.

Injection of diethylstilbestrol and estradiol benzoate reased the survival rate of normal adult male rats posed to simulated high altitudes under critical ssure-time conditions. Because a similar beneficial ect was noted in adrenalectomized rats as compared h controls, it is concluded that the beneficial effect diethylstilbestrol is not mediated exclusively by the renal glands.

JACOBSEN, Buffalo.

DROGENS AND EXPERIMENTAL MENSTRUATION IN THE MONKEY. FREDERICK L. HISAW, Endocrinology **33**:39 (July) 1943.

Evidence is furnished that testosterone propionate a weak progesterone-like action on the reproductract of the castrated and of the intact immature ale monkey.

JACOBSEN, Buffalo.

E EFFECT OF TESTOSTERONE AND ALLIED COMPOUNDS ON THE MINERAL, NITROGEN AND CARBOHYDRATE METABOLISM OF A GIRL WITH ADDISON'S DISEASE. NATHAN B. TALBOT, ALLAN M. BUTLER and E. A. MACLACHLAN, J. Clin. Investigation **22**:583 (July) 1943.

Clinical and metabolic studies of the effect of various rmones on an 8 year old girl with moniliasis, Addi-'s disease and idiopathic hypoparathyroidism are orted. These studies reveal that the administration either methyl testosterone or testosterone propionate addition to maintenance doses of desoxycorticosterone tate and sodium chloride resulted in: (1) a gain in y weight; (2) a diminution in the urinary excretion of nitrogen, potassium and sodium, and (3) a definite fall in the serum potassium concentration. No significant changes in fasting blood sugar concentration were noted. The administration of anhydrohydroxyprogesterone or of methyl androstendiol under similar circumstances prompted a decrease in urinary excretion of nitrogen but did not induce a prompt gain in body weight.

Methyl testosterone therapy did not prevent the development of symptoms and signs of acute adrenal cortical insufficiency when desoxycorticosterone acetate was withdrawn. On the other hand, testosterone propionate relieved the patient of all signs and symptoms of acute adrenal insufficiency after the discontinuation of desoxycorticosterone acetate therapy.

The lowering in the concentration of serum potassium while the patient was receiving testosterone was not associated with clinical evidences of muscular weakness or paralysis. On the contrary, the patient seemed to benefit from the testosterone as evidenced by gain in weight, growth in stature and apparent increase in strength and endurance.

[FROM THE AUTHORS' SUMMARY.]

## Diseases of the Eye

NEVUS FLAMMEUS ASSOCIATED WITH GLAUCOMA: REPORT OF A CASE IN WHICH CYCLODIATHERMY WAS USED IN AN ATTEMPT TO CONTROL THE INTRAOCULAR PRESSURE. B. Y. ALVIS and V. A. TOLAND, Am. J. Ophth. **26**:720 (July) 1943.

A boy aged 14 years had a nevus flammeus on the right side of the face which conformed in outline with the cutaneous distribution of the ophthalmic and maxillary branches of the right trigeminal nerve. The nevus was also present on the mucous membranes of the nose and throat and followed the same distribution. The right eye showed hydrophthalmos, with a tension of 43 mm. of mercury (Schiøtz). There was deep, glaucomatous cupping of the optic nerve. A corneoscleral trephine was done, but the opening closed. Vogt's cyclodiathermy was then carried out. About six months later the tension was 16.5 mm. of mercury, and corrected vision was 5/75. A Bjerrum scotoma was present in the field of vision.

W. ZENTMAYER. [ARCH. OPHTH.]

PIGMENTATION OF OPTIC DISK. DANIEL KRAVITZ, Arch. Ophth. **29**:826 (May) 1943.

Congenital pigmentation of the optic disk is uncommon in the white race, but, according to Oguchi, it is rather frequent in the Japanese. Kravitz describes the fundi in 3 cases and agrees with the opinions expressed by Duke-Elder and Mann that the pigment is the result of primitive cells of the optic stalk having regressed and acquired characteristics of pigment-forming cells in a place where other functions should have developed.

SPAETH, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

PEDAGOGIC VALUE OF ACTIVITY AND ITS CONSIDERATION IN THE EDUCATION OF THE BLIND. GREGORIO B. PALACÍN IGLESIAS, Bol. Inst. internac. am. de protec. a la infancia **15**:569 (April) 1942.

If intelligence is, as it has been stated, in a certain way the result of experience, that is, the result of the continuous assimilation of things by the mind and the adaptation of this assimilation to life, persons blind from birth or from the first years of life must be placed

in contact with the things of nature as soon as possible, so that by means of the stereognostic sense those impressions that will yield a mental synthesis most fruitful to reality and that will act as a substructure for all future mental activity can be transmitted to the brain.

According to this idea parents should avoid the habit of encouraging the quietness of the blind child and arguing that he might stumble and fall or that he needs a person to care for him. On the contrary they should incite him to act, run and play as soon as he starts walking; if possible a place in the yard, garden or field (if he lives in a rural area) should be destined for the child, in which with hygienic conditions he may play and even throw himself on the ground.

To make an adequate selection of games it is sufficient to bear in mind that, as in the case of children with sight, from 5 to 7 years is the age of the evolution of self concentration and that from 7 to 10 years of age the spirit of sociability develops.

The exercise of touch and the training of the hand should begin at the age of 3, with utilization of the material that Dr. Montessori employs in "The Children's Houses." Handicrafts have a considerable creative value, but these should not be systematized before the age of 6 or 7 years.

The introduction of agriculture and gardening and those corresponding workshop activities suitable to the blind, as for instance carpentry, have a considerable creative value but should be put off until the age of 9 or 10 years in order not to give the child a professional character until the age of 12.

FROM EDITOR'S SUMMARY.

## Skin Diseases; Allergy

A CASE OF JUVENILE XANTHOMATOSIS. FREDA K. HERBERT, Arch. Dis. Childhood **18**:41 (March) 1943.

A case of juvenile xanthomatosis is reported, with arrested growth, enlargement of the liver and the spleen, renal disease with hypertension and enormous increases in plasma phospholipins and cholesterol.

The abnormalities in plasma and tissue lipids in various pathologic syndromes and the classification of xanthomatous diseases are discussed, and the case is compared with others reported in the literature.

KELLY, Milwaukee.

A CLINICAL NOTE ON TWO CASES OF ACANTHOSIS NIGRICANS. G. A. GRANT PETERKIN and E. COLIN JONES, Brit. J. Dermat. **55**:185 (July) 1943.

The authors report 2 cases of acanthosis nigricans of the benign or juvenile form. There was no evidence of a malignant growth or of tuberculosis in either case. The cases are reported because of the rarity of this disease and because both patients were observed in a military hospital for patients with dermatologic diseases.

BLUEFARB, Chicago. [ARCH. DERMAT. & SYPH.]

THE CURE OF SCABIES AND A NEW REMEDY. G. H. PERCIVAL, Brit. M. J. **2**:451 (Oct. 17) 1942.

The cure of scabies depends on the absence of lesions and itching and the failure to find the parasite for a period of about two weeks. It is advised that a 5 per cent solution of tetraethylthiuram monosulfide is capable of curing human scabies. It is nonirritating to the human skin, and no instance of idiosyncrasy has been encountered. It is cheap and clean and does not have an objectionable odor. Its trial on a more extensive scale is suggested.

BIRDSONG, Charlottesville, Va.

## Teeth and Dentistry

A PHYSICIAN LOOKS AT SCHOOL DENTAL PROGRAM. GEORGE M. WHEATLEY, Am. J. Pub. Health **33**:1 (Feb.) 1943.

The author reviews experiences with the development of an economical school dental program among 6,4 children in eight schools for the 1937-1938 school ye (Astoria School Health Study). The school principa sent a letter to the parents of each child advising th the child have a dental examination. The priva dentists serving this area agreed to give a dental e amination to any child coming to their offices accom panied by a parent. Five thousand, six hundred a eighty-one pupils (88 per cent of the total) were e amined. Twenty-one per cent of the number examin needed no treatment. Parents of 1,859 children (29 p cent of the total) took no action. Twelve per cent d not consult a dentist, and 17 per cent did not obtain t recommended treatment. Private dentists examin two thirds of the chool children registered, supplie almost three quarters of the treatment services a were responsible for 82 per cent of the patients' co pleting treatment. The younger the child, the le successful was this plan. Only 56 per cent of the ki dergarten group reached a dentist, whereas at least per cent of the pupils above the fourth grade receiv dental examinations. Another study is quoted whi indicates that this record can be improved by means a personal interview with those parents who do n respond to a written note. This supplementary inte view, with a dental hygienist or some school heal worker, is probably necessary in the younger a groups.

The author believes that dental examinations of scho children should be done in the dentist's office rath than in the school, since 80 per cent to 90 per cent w require treatment, which is usually given in the denti office. This plan does not increase the school heal budget, utilizes the dentists of the community in t school program, trains the pupils to seek treatme facilities in the community and impresses them with t idea that payment for dental care is worth while.

PLATT, Gouverneur, N. Y.

VARIATIONS IN CALCIFICATION AND ERUPTION OF TH DECIDUOUS AND THE PERMANENT TEETH. JOHN BRAUER and MASSIS A. BAHADOR, J. Am. Dent. **29**:1373 (Aug.) 1942.

This is a consideration of calcification and erupti age in relation to chronologic age and clinical proble Roentgenograms of the dentitions of 415 children dra from four groups (diabetic, general hospital group, co genitally syphilitic and presumably well) were apprais against the chart of Schour and Massler. No differen among the four groups with respect to calcification a eruption was apparent. Sixty-six per cent of the ch dren had average schedules of calcification and eruptio when considered separately.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

FURTHER STUDIES ON THE ROLE OF VITAMIN D IN TH NUTRITIONAL CONTROL OF DENTAL CARIES IN CHI DREN. E. C. MCBEATH and W. A. VERLIN, J. A Dent. A. **29**:1393 (Aug.) 1942.

Observations on five groups of children of 40 e indicate that vitamin D in the form of cod liver oil effective in reducing the incidence of dental cari irradiated ergosterol per U. S. P. unit does not ha

effect equal to that of cod liver oil. The authors int out that in previous favorable reports on vitamin in relation to caries cod liver oil has been used, while favorable ones have been based on investigations with gosterol.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

CLINICAL AND ROENTGENOGRAPHIC STUDY OF PERIODONTIC PROBLEMS IN CHILDREN WITH SYSTEMIC DISEASE. C. HARLAN BLACKSTONE, J. Am. Dent. A. **29**:1664 (Sept.) 1942.

This is a discussion of the soft tissue and the alveolar ne conditions in patients with mild diabetes mellitus, ngenital syphilis, scurvy and aplastic anemia, supplemented with roentgenograms, case reports, photographs d a bibliography.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

RRELATION AND COMPARISON OF LABORATORY FINDINGS WITH THE CLINICAL EVIDENCE OF CARIES ACTIVITY IN A GROUP OF SIXTY-SIX CHILDREN. MARSHALL L. SNYDER, J. Am. Dent. A. **29**:2001 (Nov.) 1942.

The group was studied a little longer than two years an effort to correlate lactobacillus counts and proction of acid (reflected by changes in color in bromesol green dextrose agar) with caries activity found clinical examinations. The results suggest that a ntist might well rely on routine culturing of saliva ecimens for determining caries activity rather than on ngle clinical examinations. When caries activity is arked, changes in color appear in twenty-four hours; hen it is questionable, changes are seen in forty-eight urs; when it is absent, no color changes appear in venty-two hours. There is a general relationship tween rate of change in color and number of lactocilli per millimeter of saliva, but numbers alone are t the controlling factor. The colorimetric technic sesses the advantages of simplicity, rapidity and curacy.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

ENTAL CONDITIONS IN WHITE AND INDIAN CHILDREN IN NORTHERN WISCONSIN. LESLIE W. FOSTER, J. Am. Dent. A. **29**:2251 (Dec.) 1942.

White and Indian children having comparable geoaphic environment are compared; differences with spect to incidence of dental caries and of malocclusion e so slight as to lead the author to conclude that ile the Indians have a slight edge their contact with ilization is rapidly eliminating whatever differences y have once existed.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

## Miscellaneous

LFAMERIZINE (2-SULFANILAMIDO-4-METHYLPYRIMIDINE): I. A COMPARISON OF SULFAMERIZINE WITH SULFADIAZINE ON THE BASIS OF ABSORPTION, EXCRETION AND TOXICITY. A. D. WELCH and others, J. Pharmacol. & Exper. Therap. **77**:357 (April) 1943.

In an extensive study on experimental animals and human beings it was found that sulfamerazine is re rapidly absorbed and more slowly excreted in a re soluble form by the kidneys than sulfadiazine. In group of men an average level of 8 mg. per hundred cubic centimeters of blood was obtained in two hours and 10 mg. per hundred cubic centimeters was obtained in four hours from the small dose of 0.05 Gm. per kilogram (3.5 Gm. or 53 grains for a 150 pound [68 Kg.] man). A level of 6 mg. was maintained for twenty-four hours thereafter. These levels are much higher than those with sulfadiazine.

The possibility is offered that one or two doses of sulfamerazine daily may be sufficient to maintain a safe and an adequate concentration of the drug in the blood and the other tissues. The rapidity of absorption suggests that intravenous injection may not be necessary when it is desired to produce an adequate concentration in the blood quickly.

PILCHER, Cleveland.

METHYL SALICYLATE POISONING. ROBERT A. MACCREADY, New England J. Med. **228**:155 (Feb. 4) 1943.

The danger of poisoning by oil of wintergreen (methyl salicylate) has not been sufficiently emphasized. It is commonly used in the home and may be accidentally ingested by children, who may associate the pleasant aroma with wintergreen-flavored candy.

The usual more severe course involves vomiting, hyperpnea, diaphoresis, extreme thirst, dehydration, stupor and convulsions. In the fatal cases death commonly occurs within twenty-four hours.

Ordinary vomiting does not completely remove methyl salicylate from the stomach. Gastric lavage should be done when the patient is first seen and should be prolonged until no trace of the odor of the drug is present in the washings. If the tube is not tolerated, an automatic lavage should be employed; that is, the patient should be forced to drink huge quantities of water or of a dilute solution of sodium bicarbonate, with consequent induction of vomiting. To be adequate the process must be repeated again and again.

Of the 5 patients reported on, a boy aged 2 years was discharged on the third day; a man aged 55 recovered; a girl aged 2 years was discharged on the third day; a boy aged 3 years died two hours after ingestion; a woman aged 48 was discharged on the seventh day.

GENGENBACH, Denver.

THE NUTRIENT ENEMA. J. W. A. MACKENZIE, Arch. Dis. Childhood **18**:22 (March) 1943.

Dextrose, sodium chloride and predigested protein are absorbed from solutions introduced into the lower part of the bowel.

There is great variation in the amount of dextrose absorbed.

Absorption of sodium chloride when given by rectum is almost as great as when given by mouth.

Considerable quantities of predigested protein are absorbed from the enema.

KELLY, Milwaukee.

ABSORPTION OF DRUGS FROM THE RECTUM. J. W. A. MACKENZIE, Arch. Dis. Childhood **18**:28 (March) 1943.

The absorption of potassium bromide, sodium salicylate and sulfanilamide given per rectum has been studied.

It has been shown that when given in solution all these substances are readily absorbed from the rectum. Absorption of sulfanilamide from suppositories is poor.

Absorption of sulfanilamide is slower when the drug is given per rectum than when it is given orally.

KELLY, Milwaukee.

# Society Transactions

## CHICAGO PEDIATRIC SOCIETY

HEYWORTH N. SANFORD, M.D., *President, in the Chair*

*Feb. 15, 1944*

**A Further Report on Diphtheria Toxoid–Pertussis Vaccine, Mixed, as an Immunizing Agent.** DR. LOUIS W. SAUER and (by invitation) DR. WINSTON H. TUCKER.

In 1941 we reported before this society on the use of diphtheria toxoid and pertussis vaccine, injected either separately (simultaneously) or mixed. In the early study the 464 infants who were given the injections were all over 7 months of age. Follow-up Schick tests gave negative results for 98 per cent of the infants who had been given the toxoid and the vaccine separately and for 95 per cent of those who were given the mixed antigens. Complement fixation for pertussis was 3 plus or 4 plus in 91 per cent of the former group and in 73 per cent of the latter. Children whose initial reaction was less than 3 plus had a 3 plus or 4 plus reaction three weeks after receiving a "stimulating" dose of pertussis vaccine (2 cc. of vaccine containing 15,000,000,000 bacilli per cubic centimeter). No child who received the vaccine and toxoid is known to have acquired either disease.

The present study is a continuation of the former, and includes observations on the effects of an alum-precipitated mixture. The intervals between the doses, the total amount given and the interval between the final dose and the test of immunity were varied. Injections were started after the seventh month of life; the average age was about 8 months. More than 900 additional infants were given injections at St. Vincent's Infant and Maternity Hospital and at the Evanston Health Department Clinic. Schick tests and complement fixation tests for pertussis were performed for 729 of the infants at various intervals after the last inoculation.

For the first group diphtheria toxoid and pertussis vaccine (15,000,000,000 bacilli per cubic centimeter) were injected separately (simultaneously). The three doses were injected at intervals of one week at St. Vincent's Hospital and at intervals of three weeks at the Evanston Health Department Clinic. The reaction to the follow-up Schick test was negative in 91 per cent of the children who received inoculation at one week intervals and in 97 per cent of those who received them at three week intervals. Complement fixation for pertussis was positive (3 plus or 4 plus) in 69 per cent of the children inoculated at intervals of one week. Seventy-one per cent of the children showing initial reactions that were less than 3 plus had 3 plus or 4 plus reactions after receiving a "stimulating" dose of 2 cc. of pertussis vaccine (15,000,000,000 bacilli per cubic centimeter). Pertussis complement fixation was positive (3 plus or 4 plus) in 97 per cent of the infants inoculated at three week intervals. Children who showed initial reactions that were less than 3 plus had 3 plus or 4 plus reactions after receiving a "stimulating" dose of pertussis vaccine (2 cc. of vaccine containing 15,000,000,000 bacilli per cubic centimeter).

For the second group the diphtheria toxoid and pertussis vaccine (15,000,000,000 bacilli per cubic centimeter) were mixed. The injections were given at intervals of one week at St. Vincent's Hospital and at intervals of three weeks at the Evanston Health Department Clinic. The reaction to the follow-up Schick test was negative in 91 per cent of the children inoculated at intervals of one week and in 97 per cent of those inoculated at intervals of three weeks. Complement fixation for pertussis was 3 plus or 4 plus in 66 per cent of the infants who received injections at one week intervals. Because the response to immunization in this group was low, inoculation at intervals of one week was discontinued. A total of 6 cc. of toxoid and vaccine (1, 2, 3 cc. or 2, 2, 2 cc.) when injected at intervals of four weeks gave approximately the same immunity as 7 cc. injected in three doses at intervals of three weeks. Pertussis complement fixation was 3 plus or 4 plus in 72 per cent of the infants given injections at three week intervals. Ninety-five per cent of those whose reaction was less than 3 plus had 3 plus or 4 plus reactions after receiving a "stimulating" dose of pertussis vaccine (2 cc. of vaccine containing 15,000,000,000 bacilli per cubic centimeter). In no instance was a local or systemic reaction severe.

For the third group an alum-precipitated mixture of diphtheria toxoid and pertussis vaccine (10,000,000,000 bacilli per cubic centimeter) was used. One cubic centimeter was injected three times in alternate arms at intervals of one week at St. Vincent's Hospital and at intervals of three or four weeks at the Evanston Health Department Clinic. The reaction to the Schick test was negative in 83 per cent of the infants inoculated at intervals of one week and in 98 per cent of those inoculated at intervals of three weeks. Complement fixation for pertussis was positive (3 plus or 4 plus) in 77 per cent of the one week interval group and in 92 per cent (or 94 per cent) of the three week interval group. Eleven infants at St. Vincent's Hospital had a total of 14 sterile abscesses, and 8 at the Evanston Health Department Clinic had sterile abscesses in spite of deeper injections. All infants with reactions of less than 3 plus to the complement fixation tests had 3 plus or 4 plus reactions after receiving a "stimulating" dose of 2 cc. of pertussis vaccine (15,000,000,000 bacilli per cubic centimeter).

*Conclusion.*—The length of the interval between the doses had a definite effect on the degree of immunity developed. In each of the three groups (those receiving separate toxoid and vaccine administered simultaneously, mixed antigens and alum-precipitated mixed antigens) the Schick test and the complement fixation test for pertussis showed that the immunity was higher when the doses were injected at three or four week intervals than when they were injected at one week intervals. The immunity as revealed by Schick tests and by complement fixation tests for pertussis was not as high after the administration of mixed diphtheria toxoid and pertussis vaccine as when the antigens had been injected separately or when the alum-precipitated

mixture had been used, but no child given plain or alum-precipitated mixed antigens since 1938 is known to have contracted either disease. The fact that 6 per cent of the 339 infants given injections of alum-precipitated mixture had sterile abscesses makes us favor plain mixed antigens. A "stimulating" dose of 2 cc. of plain pertussis vaccine (15,000,000,000 bacilli per cubic centimeter) produced a sharp increase in pertussis complement fixation. The "stimulating" dose may be injected months after the original immunization. An opportune time may be when the child is vaccinated against smallpox or when he enters nursery school or after known exposure.

**Retrolental Fibroplasia.** T. L. TERRY, M.D. (by invitation).

The presence of embryonic connective tissue in the meshwork of the persistent hyaloid arterial system behind the crystalline lens as a result of improper development of the inner eye is a disease entity which I call "retrolental fibroplasia." The condition usually develops three to five months after birth in extremely premature infants. It occurs in some 12 per cent of infants whose weight at birth is 3 pounds (1,300 Gm.) or less, according to Dr. Stewart Clifford. Ninety-seven cases have been recorded. The basis for the disease in the premature infant lies in the fact that the hyaloid vascular system is still functioning at birth if the infant is even four weeks premature.

The cause for the vascular persistence and the development of embryonic connective tissue has not been found, although diligent search has been made, with consideration of all logical factors, including precocious exposure to light, low postnatal temperature, Rh factor, vitamins, hemorrhage and many others.

Repeated attempts to produce this disease or to cause precocious disappearance of the hyaloid vascular system in literally hundreds of young opossums (while within the marsupial pouch) and newborn rats have failed.

Because of sluggish resorption of this abnormal tissue, retardation of growth of the eye and complications such as glaucoma and separation of the retina, the ultimate prognosis for vision is extremely bad. Radical surgical procedures and roentgen therapy have proved harmful. However, surgical attempts to produce a better blood vascular connection to the ciliary body appear to give some beneficial effect.

The discovery of a method of prevention and a possible cure probably depends on establishment of the cause, for which the pediatrician may be in a better position than the ophthalmologist.

DISCUSSION

DR. E. V. L. BROWN: Fibroplasia is difficult to differentiate from glioma (neuroblastoma) retinae. The chief symptom of both conditions is a white reflection behind the pupil. This condition is usually first observed by the mother four to six months after birth and comes from vascular tissue behind the lens.

From 1935 through 1940, 21 eyes were removed for glioma at the University of Chicago Clinics on my advice. Four of these were fibroplastic, and possibly 2 others were.

In the past three years Dr. Terry has seen 99 fibroplasias in prematurely born infants in and around Boston. According to him, 1 out of 10 babies born before the seventh month and weighing less than 3½ pounds (1,500 Gm.) is blind from fibroplasia in one or both eyes. Incubator care, widely introduced in the early 1930's, has doubtless saved many babies; but nature seems to exact a high price in this matter, a price mitigated only a little by the fact that now, through Dr. Terry's discovery of the relationship of prematurity to fibroplasia, we are able to avoid the needless enucleation of some already blinded eyes.

DR. J. M. DONEGAN: It should be emphasized, I believe, that this condition is not simply a rare and interesting anomaly which occurs in Boston. Several months ago I had the pleasure of visiting Dr. Terry and seeing the intensive clinical and laboratory investigation he has been conducting. After he had shown me 16 infants with various manifestations of this disease, I was certainly convinced that it occurred there. Many ophthalmologists in Chicago, including Drs. Gamble, Gifford, Gradle, Kronfeld, Krause, Fowler and Allen, can attest that it occurs here with considerable frequency.

Since Dr. Terry's original paper appeared, the majority of ophthalmologists have seen examples of this condition. Prior to that time undoubtedly the condition was not recognized in many instances. Several of the eyes I have examined contained fibroblastic overgrowths behind the lens rather than retinoblastomas. These eyes had been clinically diagnosed as involved by neuroblastoma retinae and were enucleated from premature infants born as long ago as 1935. It is hoped that once this condition has been brought to the attention of the pediatricians and they have become interested in the problem much more can be accomplished in determining the cause, the frequency and the real nature of the disease.

Through Dr. Sanford's interest and help, we at Presbyterian Hospital have been studying all prematurely born infants weighing less than 5 pounds (2,250 Gm.) at birth. An attempt is made to follow these infants from shortly after birth, with particular reference to the amount of vision determinable, the relative size of the globe and the cornea, the depth of the anterior chamber, the color and development of the iris, the presence of vascular remnants on the iris, the size and reaction of the pupil, the clarity of the media, the persistence of any or all portions of the hyaloid system and the appearance of the fundus. In time we hope to obtain some clue to the causation and manner of development of the disease. Prophylactic and therapeutic measures must, of course, await future developments.

DR. EARLE B. FOWLER: I have been interested in these cases because shortly after reading the first published report I observed a patient with this condition at Presbyterian Hospital, and fairly recently I saw a second patient. Of course I am now interested in every premature infant arriving there. I wonder how many more premature infants are saved now as compared with former years. Can it be presumed that this condition is seen more often because earlier premature infants are now saved, or is it a new disease?

DR. JULIUS H. HESS: I must confess that I have seen a good many premature infants weighing less than 3 pounds (1,300 Gm.) at birth, and it is surprising how few bad eyes there were among them. In 1 infant weighing 2 pounds 10 ounces (1,200 Gm.) at birth, I noted a condition involving both eyes which might have been that described by Dr. Terry. It was first noted when the infant was 5 months of age. Dr. Terry had an opportunity to see this child today and might give an opinion. But it is remarkable how few patients I have seen personally that might fit into the

group, notwithstanding the fact that I have followed for a number of years a large group of premature children, some of whom are now 16 or 17 years old.

Is it possible that the endocrine system may be an important factor in development of the condition?

DR. SANFORD GIFFORD: I think I have seen retrolental fibroplasia in as many as 25 infants. The condition occurred unilaterally in 1 infant born at full term; there was an opaque mass behind the crystalline lens, which at the time was considered to be a glioma, and the eye was enucleated. That case was reported. When the true nature of the condition was understood, after enucleation, a review of the record showed that the cornea in this eye had been observed to be smaller than that in the other eye. It seems to me that one can be sure that an abnormally small eye does not contain a glioma.

Since Dr. Terry has been writing about fibroplasia in premature infants, I have seen about 20 patients with the disease in the Chicago area. There were 3 or 4 each at the County Hospital and at the clinics of Northwestern University Medical School, and I have seen a number in consultation. Some of the patients were brought because of the diagnosis of glioma, for which enucleation had been recommended. I have seen enough clearing in 1 or 2 patients to permit the observation of the retinal folds that Dr. Terry has described, but in most instances the membrane has been so dense that it was difficult to see the retina.

DR. HEYWORTH N. SANFORD: Referring to Dr. Fowler's question as to whether this is a new disease or whether more premature infants are being saved: When Ethel Dunham made her survey of premature infants, published in 1935, she found that the average mortality for premature infants in hospitals throughout the United States in the early 1930's was about 26 per cent. In Chicago from 1931 to 1937 the mortality for premature infants at Lying-In Hospital was 20.7 per cent. Since 1938 there has been a drive in Chicago to lower the mortality in this group of infants. I do not know the percentage for the past year, but I venture to say that certainly in most hospitals in Chicago it is well below 20 per cent; most of the decrease has been in the group of extremely small premature infants, those weighing less than 3 pounds (1,300 Gm.). Premature infants that once would have been born in hospitals without facilities for special care or in homes and would have died shortly are now taken to hospitals with special units for the care of premature infants and are saved. I wonder if there are not more early premature infants to study under today's conditions.

DR. THEODORE L. TERRY: Dr. Fowler suggests that perhaps this fibroplasia is not a new disease. That may well be true but if so the disease entity was formerly incompletely described, and many of the symptoms of the condition have only recently been observed. The decrease in the mortality of prematurely born infants may explain the apparent "epidemic" of the condition. Although I know little of the technicalities of keeping premature infants alive, I had gained the impression, which appears erroneous, that there had been no important advances in saving premature infants during the past ten years, although I was aware that the technic was improving. Certainly this disease is much more frequent in the past five years than in the preceding four. I am sure that an ophthalmologist who saw more than 1 premature infant with this disease within twelve months could not help but realize that the condition was related to prematurity.

That Dr. Hess has seen few cases brings to mind the possibility that this condition may originate only in certain hospitals. For instance Goldberg in Baltimore found 6 cases in 1 hospital, and so far as he knew no other cases had arisen in that city at that time. Can this mean that there are certain local hospital practices which may induce the disease? The patient Dr. Hess was kind enough to let me see this afternoon had an immature cataract of rather rare type as the cause of poor vision. The condition is probably related to a disturbance of calcium metabolism and possibly had its beginning during or before the third month of fetal development. At a somewhat more advanced stage this cataract would give a picture similar to that of fibroplasia.

Consideration has been given to endocrine disturbances as a cause for retrolental fibroplasia. The premature infant living outside of a maternal environment may have endocrine dysfunction of important amount. Only recently I have learned from Dr. Snyder of the department of anatomy of Harvard Medical School—whom some of you perhaps knew when he was at the University of Chicago—that he is convinced that endocrine function begins when the endocrine glands have reached histologic maturity. Since I have obtained this information only recently, I have had no opportunity to reevaluate the endocrine factor in relation to this disease.

I am surprised at the number of cases Dr. Gifford has observed. He brings out, as did Dr. Brown, the tremendous importance of arriving at the proper diagnosis in order to avoid needless enucleation and perhaps to retain for the infant some vision.

Thank you for the opportunity of letting me describe my impression of this disease. Of course time will show which of my assumptions are incorrect.

# Book Reviews

**The Kenny Concept of Infantile Paralysis and Its Treatment.** By John F. Pohl, M.D., and Sister Elizabeth Kenny. Price, $5.00. Pp. 366, with illustrations. St. Paul: Bruce Publishing Company, 1943.

It is difficult to evaluate the methods recommended or the treatment of infantile paralysis in this book y Sister Kenny and Dr. Pohl. Only time can do this. However, some facts are obvious. Sister Kenny has emonstrated that immobilization in the acute stage f the disease is unnecessary. This idea is not original; thers have urged that immobilization be discarded. ome men in the United States have been treating eir patients without immobilization for years, although is practice had never been accepted by the medical rofession until the advent of Sister Kenny. She hould be given credit for having the idea accepted, ut equal credit is due the National Foundation for nfantile Paralysis, Inc., for giving her the opportunity o demonstrate her ideas. Without its aid, she too ould not have been heard.

It is not certain whether Sister Kenny gets good sults because of the meticulous application of good reeducational principles or because of the hot compresses which she insists on using. My deduction would be that reeducation is the chief reason. Her statement that this type of heat is better than any other is something that must also be checked. Sister Kenny herself probably realizes that her work has to be verified.

One wonders why the authors introduce such bizarre ideas of physiology in order to explain certain functions that could be explained simply, without straining the imagination and without the introduction of such complex terms as mental alienation, incoordination and spasm. The fact that these physiologic beliefs have not been accepted does not in any way detract from the usefulness of Sister Kenny's regimen.

There are things about Sister Kenny's dictums that can be questioned. Her concept of pain, spasm and the cause of spasm does not seem to fit the facts. However, it must be admitted that there is progress outlined in this volume. It is a good book, although not a classic. Much that has been written cannot be concurred with, but pediatricians treating this disease can read the book with great benefit.

# Directory of Pediatric Societies *

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### Associação Paulista de Medicina, Section on Pediatrics

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Paulo de Barros Franca, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

### British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

### Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

### Sociedad Cubana de Pediatria

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

### Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

### Sociedad Venezolana de Puericultura y Pediatria

President: Dr. E. Santos Mendoza.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas.

### Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

### Uruguyan Society of Pediatrics

President: Dr. Jose Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Alfredo Ramon Guerra, Paysandú 824, Montevideo.

## NATIONAL

### American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

### American Academy of Pediatrics

President: Dr. Franklin P. Gengenbach, 1850 Gilpin St., Denver, Colo.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

### American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

### American Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

### Canadian Society for the Study of Diseases of Children

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

### Society for Pediatric Research

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

## SECTIONAL

### Intermountain Pediatric Society

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

### New England Pediatric Society

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

### Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary. Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

## STATE

### Alabama Pediatric Society

President: Dr. Amas Gipson, 948 Forrest Ave., Gadsen.
Secretary-Treasurer: Dr. Ruth Berrey, 2021-6th Ave. N., Birmingham.

### Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

### Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. William C. Deamer, University of California Hospital, San Francisco.
Secretary: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco.

### Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. T. F. Davenport, 104 Ponce de Leon Ave. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

### Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. A. Clement Silverman, 608 E. Genesee St., Syracuse.
Secretary: Dr. Albert G. Davis, 307 Gas and Electric Bldg., Utica.

### Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

### Michigan State Medical Society, Pediatric Section

Chairman: Dr. Charles F. McKhann, University Hospital, Ann Arbor.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

### Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

### Nebraska Pediatric Society

President: Dr. E. W. Hancock, 820 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. John M. Thomas, 1102 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

### New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

### North Carolina Pediatric Society

President: Dr. Arthur H. London, 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, 604 W. Chapel Hill St., Durham.

### Oklahoma State Pediatric Society

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

### South Carolina Pediatric Society

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, Wade Hampton Office Bldg., Columbia.

### Texas Pediatric Society

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

### Virginia Pediatric Society

President: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond.

### West Virginia State Medical Society, Section on Pediatrics

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

## LOCAL

### Academy of Medicine of Cleveland Pediatric Section

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

### Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

### Bronx Pediatric Society

President: Dr. Harry J. Cohen, 1975 Walton Ave., New York.
Secretary: Dr. Walter Levy, 12 E. 88th St., New York.
Place: Concourse Plaza Hotel, 161st St., and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

### Brooklyn Academy of Pediatrics

President: Dr. Harry A. Naumer, 37–8th Ave., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

### Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

### Central New York Pediatric Club

President: Dr. Edward J. Wynkoop, 501 James St., Syracuse.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places:: Various cities in New York. Time: Third Tuesday of April and September.

### Chicago Pediatric Society

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, Inclusive.

### Cincinnati Pediatric Society

Secretary: Dr. T. Selkirk, 3530 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.

### Dallas Pediatric Society

President: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort, Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

### Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Abraham M. Litvak, 1145 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

### Memphis Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellevue Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Howard Craig, 175 E. 79th St., New York.
Secretary: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northern California Affiliates

President: Dr. Crawford Bost, 400 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

### Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 625 N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

### Philadelphia Pediatric Society

President: Dr. Carl Fischer, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in January, March, May and November.

### Pittsburgh Pediatric Society

President: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown, Pa.

Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh.

Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

### Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Louise Galvin, 214 S. Boulevard, Richmond, Va.

Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.

Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Jerome Diamond, 508 N. Grand Ave., St. Louis.

Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.

Place: St. Louis Medical Society Bldg. Time: First Friday of each month from November to June.

### Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.

Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

### Southwestern Pediatric Society

President: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.

Secretary: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.

Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

### Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.